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EFFECT OF FABRICATION TECHNIQUES ON DEGRADATION AND DRUG RELEASE PROFILE OF POLYANHYDRIDES

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ABSTRACT

The degradation of poly (carboxy phenoxy propane (CPP) - co – sebacic acid (SA)) samples prepared from cold compression moulding and injection moulding, and poly (sebacic acid) sample from solvent evaporation technique was monitored through various means. Different forms of polyanhydride samples (discs, rods and microcapsules) were expected to give different degradation behaviours and hence the release patterns of the drug. The degradation behaviour was monitored through Fourier Transform Infra-Red (FTIR), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Variable Pressure Scanning Electron Microscopy (VPSEM) techniques. Drug release was evaluated through the usage of UV spectroscopy techniques. Results pointed to the fact that the disc samples possibly showed a combination of both surface and bulk erosion degradation mechanism whilst purely surface erosion was demonstrated for rods prepared from the injection moulding technique. The poly (sebacic acid) microcapsules on the other hand possessed a 3-stage degradation behaviour which consisted of the removal of the amorphous region followed by the more crystallized counterpart. Zero order drug release pattern was thought to be shown by both compression and injection moulding techniques. The microcapsules on the other hand demonstrated a slightly burst drug release in the earlier degradation stage followed by a slower release at later stage. It is interesting to know how fabrication of the samples can alter the degradation behaviour of polymer and drug release pattern.

Keywords: Polyanhydride, Degradation, Controlled release, Fabrication

INTRODUCTION

Degradation and erosion are mostly important for biodegradable polymers in such they reveal the drug release mechanism of the incorporated drug. Degradation which is the process of chain cleavage can be investigated by following the molecular weight of a polymer during degradation period. On the other hand, erosion is the sum of all processes leading to the loss of mass from a polymer matrix. It is important to note that degradation is not mandatory for polymer matrix to erode. Dissolution process might contribute to erosion as well if the polymer is partially soluble inside the erosion medium. Conversely, if the polymer has degraded completely, erosion does not necessarily take place [1].

Investigation of degradation and controlled drug release behaviour of polyanhydride is presented in this work, taking into account how fabrication of the samples can influence both degradation and drug release profile. Polyanhydride is known to undergo a surface erosion mechanism on disc samples of reasonable thickness. Such work reveals the time frame on which degradation occurs and therefore yields precious information on the expected time over which the drug would be released. With increasing or decreasing dimensions or varying device shapes, the drug release profile depends on other processes in addition to degradation such as water diffusion into the matrix. If the water diffusion is slow, degradation will be affected tremendously because lack of water could prevent further degradation at the core of the matrix. Thus the degradation could take place at a much slower pace [1].

Fabrication of a controlled release device is a process of turning a bioactive agent into a finished product that exhibits a controlled delivery of the bioactive agent to a host site. The controlled delivery can be of various means which include continuous delivery, extended delivery, delayed delivery, pulsatile delivery or triggered delivery [2].

Several important factors have to be considered when developing a polymer for controlled delivery and these include biocompatibility and toxicology of the degradation products, chemical, physical and mechanical properties of the polymer, suitable solvents, processing requirements and thermal transition temperatures of the polymer. The relative importance of these factors varies depending on the application. A product containing thermally sensitive active agents may not require a thermal processing technique as this would cause decomposition of the polymer and reduce efficacy of the used drug [2].

This work utilized three processing techniques in producing three shapes of the delivery device. Disc shape samples were produced using cold compression moulding technique. In cold compression moulding, the material to be molded was placed in a mold at room temperature in the form of a loose powder [3,4]. An excess of several percentage was usually added to the mould to ensure complete filling. The mold was then closed and sufficient pressure was applied to force the material into the mold cavity at room temperature. This technique produced disc of 2 mm thickness with 15 mm diameter.

Rod shape samples were produced from injection moulding technique [5]. In this process, the mould was split to allow part removal and kept closed during injection by an appropriate clamping force. The mould was filled by forcing a precompounded molten polymer into the mould. The injection cycle utilizing the use of a reciprocating screw produced rod samples of 25 mm length with 12 mm diameter.

The last techniques employed the solvent processing method producing microcapsules [6]. This was a process whereby particles of an active agent were surface-coated to provide changes in the physicochemical properties of the active agent. Emulsification – solvent evaporation was used in this work which produced microcapsules of 30 µm.

With various processing techniques employed in producing three different shapes of device namely discs, rods and microcapsules, it is interesting to know the effect of this processing technique towards the degradation behavior of polyanhydride and how it controls the release kinetic of the incorporated drug. Thus, this issue is addressed in this paper.

MATERIALS AND METHODS

Injection moulding and cold compression moulding samples were prepared from poly(1,3-bis(p-carboxy phenoxy) propane – co – sebacic acid) (20:80) (poly(CPP-co-SA) that was synthesized following melt polycondensation method [7]. Samples in rod form of about 180 mg polymer of each, with length of approximately 12 mm and diameter of 25 mm were first prepared using the injection moulding technique (Capillary Torque Rheometer, CFT500T

Shidmazu, Japan). The flow temperature used was 56.4 °C with polymer viscosity of 6.418 × 10^3 Pa.s. On the other hand, discs samples of 0.25 g mass, diameter of 20 mm and thickness of 1 mm were prepared using the cold compression moulding technique (Gabbrielli Crometro CR 415-E2 hydraulic press, Naniwa Gousei Co., Ltd., Japan). Degradation and drug release of both types of samples were performed in 25 ml 0.01 M, pH 7.4 of phosphate buffer saline (PBS), Amresco (Solon, Ohio) at 37 °C with agitation of 20 rpm to simulate the physiological temperature of the plasma fluid. Steady drug release is expected in neutral buffer, hence the selection of pH 7.4. Lower pH will normally results in rapid drug release whilst alkaline environment exerts slower drug release which reveals the choice of pH. Slow agitation is needed in this work to prevent accumulation of drug at the sample surface and to maintain sink condition. The samples were removed and dried in vacuum oven for 3 days at 40 °C.

Poly (sebacic acid) (Acros Organics, Thermo Fisher Scientific, USA) microspheres were prepared by double emulsion technique. 25 mg of cis-platin was first dissolved in 1.25 ml dimethyl formamide (DMF) (Acros Organics, Thermo Fisher Scientific, USA). Polymer solution was prepared by dissolving 500 mg of poly (sebacic acid) in 2 ml chloroform. The drug solution was poured into polymer solution and sonicated for 2 minutes. The mixture solution was immediately transferred to 0.02 w/v % of PVA solution and homogenized at 3,500 rpm for 5 minutes. Evaporation of solvent was carried out under gentle stirring for 2 hours. Finally, the poly (sebacic acid) microspheres were obtained after centrifugation at 10,000 rpm for 5 minutes before being freeze dried for 24 hours. Degradation and drug release work were performed similar to those of disc and rod samples.

The physical appearance of the samples were captured through Extended Pressure Scanning Electron Microscope (EPSEM, Carl Zeiss, EVO LS 10, UK), with pressure of 273 Pa and relative humidity of 31.3 % using cold stage. The thermal properties of the samples were determined on a Mettler Toledo (DSC 821e, USA) equipped with STARe Software. Samples were subjected to a heating rate of 10 °C/min over a single heating cycle from 25 °C to 200 °C under nitrogen atmosphere. Water uptake and mass loss were measured using gravimetric method following the equations below:

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

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

in which, 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 determined by utilizing the Fourier Transform Infrared (FTIR, Nicolet Magna IR 560 Spectrometer, New York, USA). Samples were prepared with KBr powder into pellet form and analyzed using OMNIC software. UV spectrophotometer, (Perkin Elmer UV-vis, USA) equipped with Lambda 25 software was used for monitoring the drug release profile. X-Ray Diffraction (XRD) profiles of the samples were taken on a (Bruker D8 Advance, USA) 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. All data were collected in triplicates and treated with ANOVA and P value of <0.05 was considered significant.

RESULTS AND DISCUSSION

Physical appearance of degrading samples from variable pressure scanning electron micrographs

The injection moulding technique applied a low heat of 56.4 °C to allow the polymer to flow before filling in the mould. This low heat enabled the copolymer powder to fuse together forming a closely packed polymer rod as seen in the EPSEM micrograph (Fig. 1, Day 0). A rather smooth polymer surface was seen with no sign of cracks and fissures. The rods were dense and uniform in structure. As early as 4 hours, some thin line of cracks appeared on the surface of the sample and on later degradation period the thin line of cracks developed into larger cracks and propagated throughout the sample's surface. This observation was obvious on day 1, day 2 and day 4. On day 6, the cracks were getting deeper and on day 8 these cracks were about to be peeled off from the surface of the samples. These cracks layers were eventually being removed from the sample's surface exposing the layer underneath which had a rough texture. This phenomenon was observed on day 10 and day 12.

Fig. 2 demonstrated the micrographs of the degraded copolymer discs prepared from the compression moulding technique. Unlike the injection moulded rod samples, large cracks had already appeared on the degraded samples on earlier degradation time points starting from day 2. The cracks were very deep and were peeled off from the surface on day 5. Similar large cracks were quickly developed before it was being removed on longer degradation time points as demonstrated from micrographs taken on day 8 until day 12. Here, the underneath layer which was being exposed, showed quite a rough texture with pores indicating possible loss of the polymer. The pores were however not observed in the micrographs of the injection moulded samples. It was also possible that the compression moulded samples possessed slightly loose packing materials as opposed to the tightly bound polymeric materials in the injection moulded samples. Hence, this could help in loosing the polymeric materials once it was in contact with the degradation buffer.

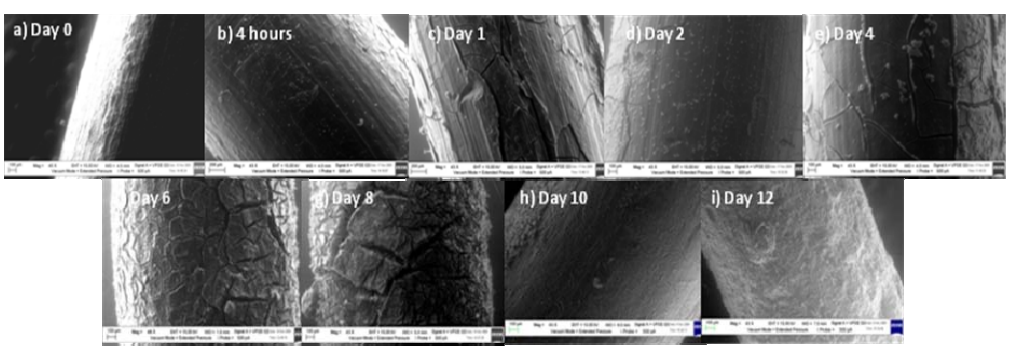


Fig. 1: Extended Pressure Scanning Electron Microscope images of poly(1,3-bis(p-carboxy phenoxy) propane – co – sebacic acid) (20:80) (poly(CPP-co-SA)) in rod form throughout the degradation period.

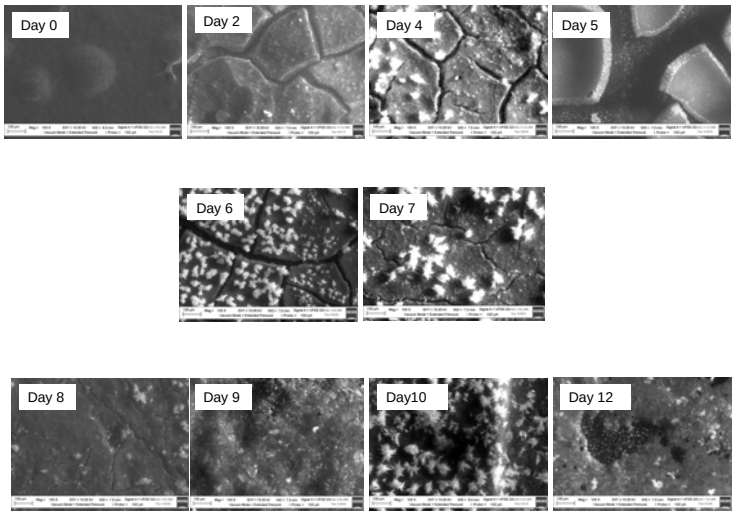
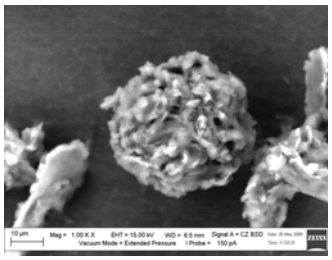


Fig. 2: Extended Pressure Scanning Electron Microscope images of poly(1,3-bis(p-carboxy phenoxy) propane – co – sebacic acid) (20:80) (poly(CPP-co-SA)) in discs form throughout the degradation period.

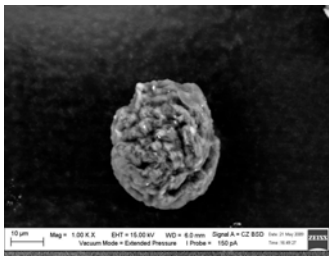
The blank microspheres prepared from the synthesized poly (sebacic acid) exhibited a rather rough polymer surface even on day 0 (Fig. 3a-c). This indicated that the synthesized polymer was quite crystallized and can be observed from the spherullitic structure on the surface of the microspheres. Small pores with rough surfaces were already visible even at the initial degradation stage.

It was thought that these microspheres underwent 3-stage degradation mechanism. As the microspheres were in contact with the degradation medium, development of pores can be seen as early as 8 hours for both blank and drug loaded samples (Fig. 3). The pores were seen to propagate and larger in size whilst the size of the microspheres reduced quite significantly throughout the degradation period. Stage 1 depicted a size range of approximately 30 – 40 µm in the first 3 days (Fig. 3a). Stage 2 depicts a gradual decrease in size of 15 – 30 µm on the following day 4 to day 8 (Fig. 3b). Besides bigger and distinctive pores, the microspheres appeared to undergo a rupture process which rendered the smaller size obtained. The microspheres at the final stage (Fig. 3c) from day 9 to day 15 experienced a major rupture in which the spherical microsphere shape was no longer retained at this stage.

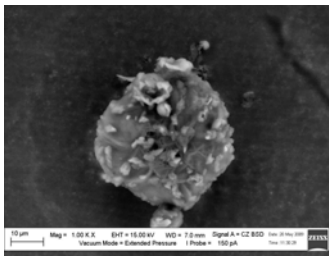
a)



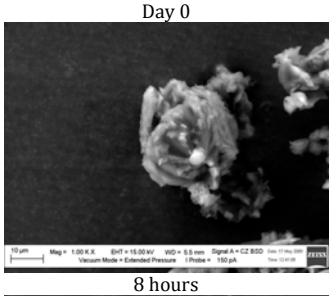
Day 0



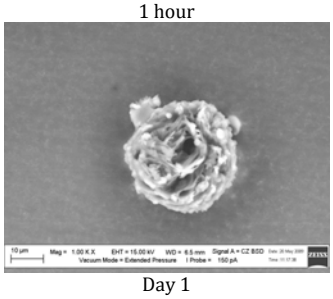
1 hour



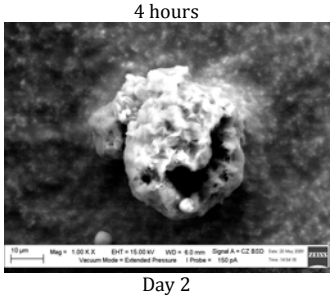
4 hours



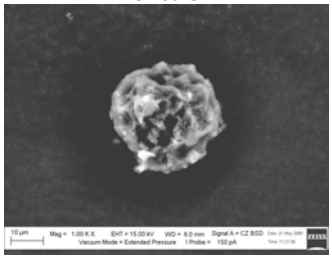
8 hours



Day 1

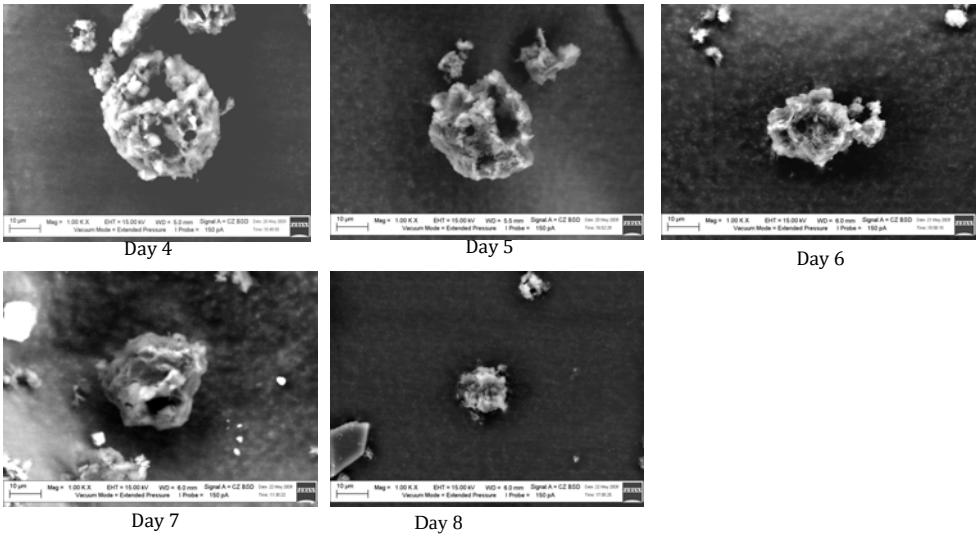


Day 2



Day 3

b)



c)

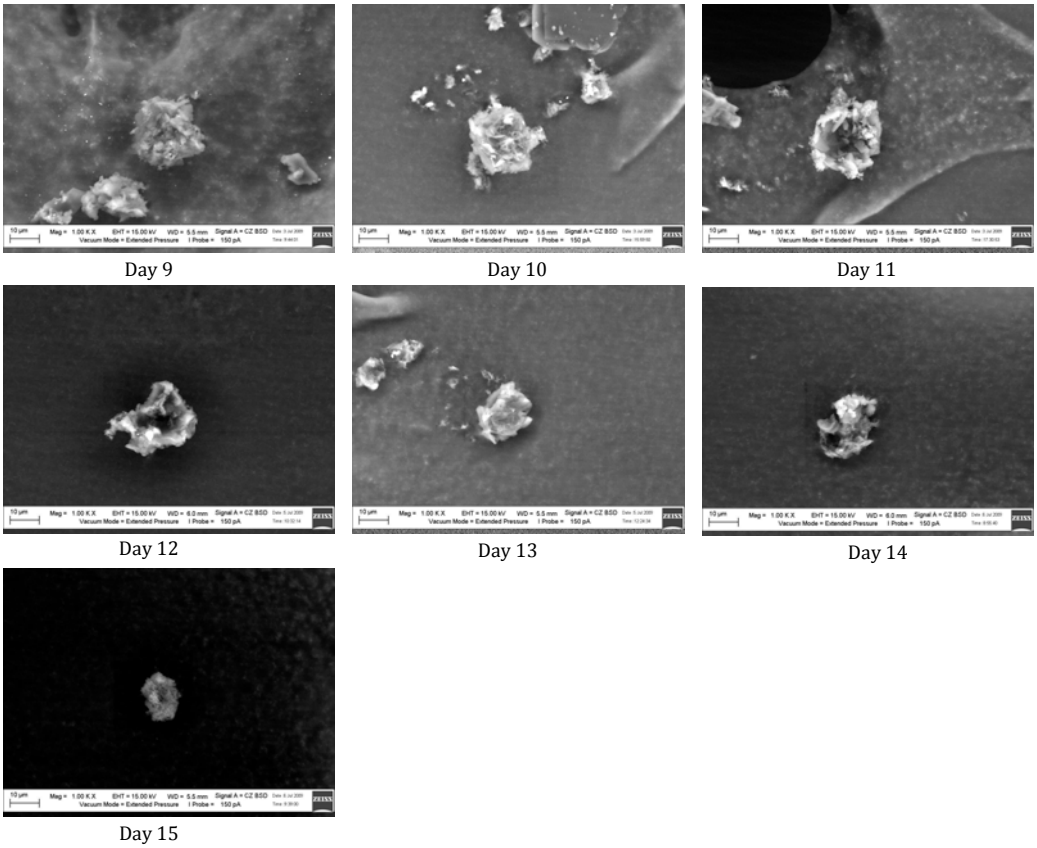


Fig. 3: Extended scanning electron micrographs of degraded blank microspheres of poly (sebacic acid) as a function of time with size range of a) 30 – 40 µm (stage 1), b) 15 - 30 µm (stage 2) and c) 10 – 20 µm (stage 3).

Water uptake and mass loss

Degradation of the copolymer occurred once water molecule from the degradation medium cleaves its anhydride linkages forming the acidic monomers of sebacic acid and CPP. The monomers will diffuse into the degradation medium once they have reached their critical molecular weight. The process that consisted of water uptake and mass loss was featured in Fig. 4. The injection moulded samples showed an increase of about 10 wt.% of water uptake on the first 2 days to 20 wt% on day 4. Water uptake was quite

constant on longer degradation period. The mass loss showed a similar pattern in which about 15 wt% of mass was lost on the first 2 days and it increased to 20 wt% on day 4. After day 5, the mass loss was also quite constant throughout the degradation time. When comparing these data with the ones of cold compression moulded samples, one can say that there is not much difference in terms of the pattern of water uptake and mass loss, only that the cold compression moulded samples showed a slightly higher water uptake and mass loss throughout the degradation period. This was again related to the relatively loosely packed polymer powder in compression moulded discs samples when compared with the injection moulded ones.

Using the 3-stage degradation model from the microscopy analysis, similar observation can be made for mass loss profile of the microspheres featured in Fig. 5. In stage 1, the blank microspheres displayed a rapid loss of polymer of 49 wt % in the first hour, followed by a slow release of polymer from 4 hours to day 4. Quite a similar pattern of polymer loss was demonstrated at stage 2 and 3. The rapid loss of the polymer demonstrated a sign of a fast erosion of the polymer at a shorter degradation time which was thought to occur from the amorphous part of the polymer. As water was absorbed, it quickly cleaved the anhydride bonds forming the sebacic acid monomers and these monomers upon reaching their critical molecular weight will diffuse into the degradation medium.

The slightly slower mass loss in stage 3 can be attributed to the slow loss of the crystalline phase of the sample. Rapid degradation consisted of the loss of the amorphous material and this would result in water diffusion into the pores and channels created by the loss of the polymer. However, it was not easy for the water to penetrate into the crystalline part for degradation to occur which demonstrated the slow mass loss in the profile on longer degradation time point.

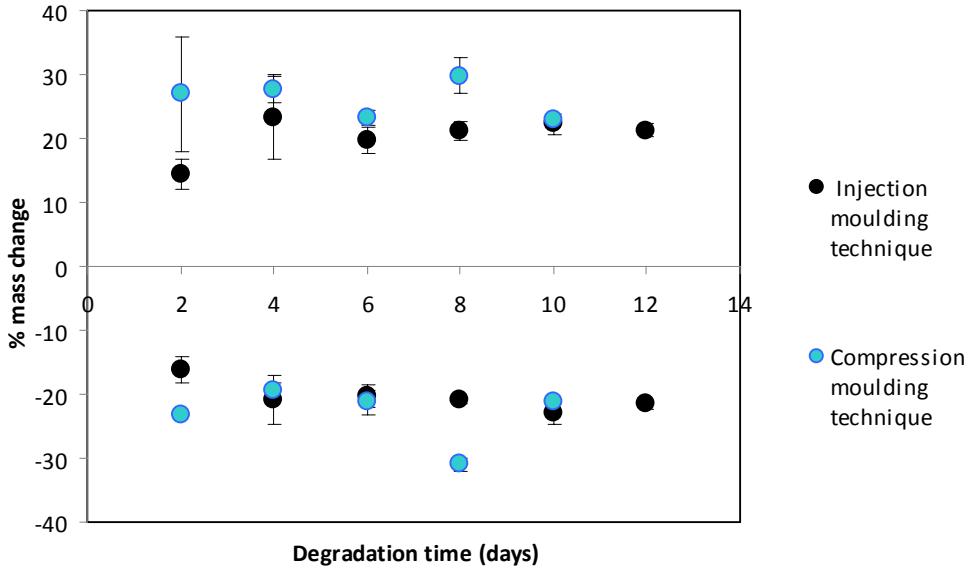


Fig. 4: Water uptake and mass loss profile of poly(CPP-co-SA) discs and rods samples as a function of degradation time (n=3).

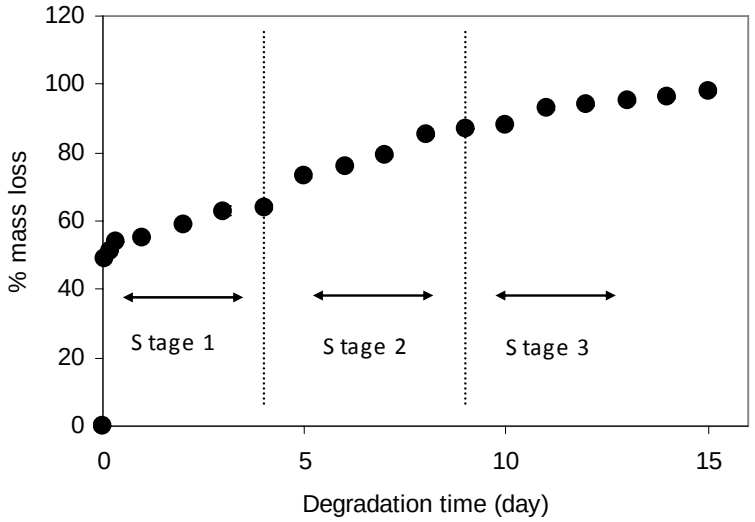


Fig. 5: Mass loss of degraded poly (sebacic acid) microspheres blank and drug loaded plotted as a function of degradation time (n=3).

Changes of pH

The degradation behavior of both injection moulded and cold compression moulded samples was again manifested in both the pH (Fig. 6) and monomer release profiles (Fig. 7). The accumulation of the degraded acidic monomeric products of sebacic acid and CPP in the degradation medium caused the reduction in pH of the degradation medium. CPP monomer which contained aromatic benzene group was detected by UV-vis spectrometer and the cumulative release of the monomer was plotted against time (Fig. 7). As expected, a slower pH reduction was seen for samples prepared from the injection moulded samples (Fig. 6) accompanied by a much lower cumulative release of CPP monomer was detected (Fig. 7) when compared with the cold compression molded samples. These data corresponded very well with the slower water uptake and mass loss observed in Fig. 4 and the late appearance of major cracks on the samples' surface of injection moulded samples as shown in the EPSEM micrographs (Fig. 1).

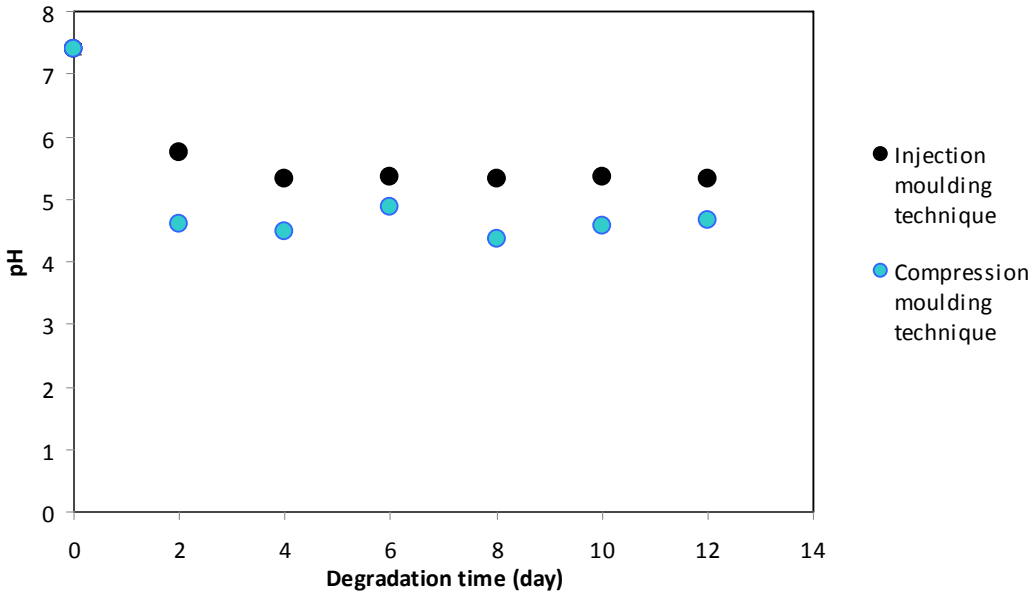


Fig. 6: Change of pH of degradation medium of poly (CPP-co-SA) (20:80) as a function of time (n=3).

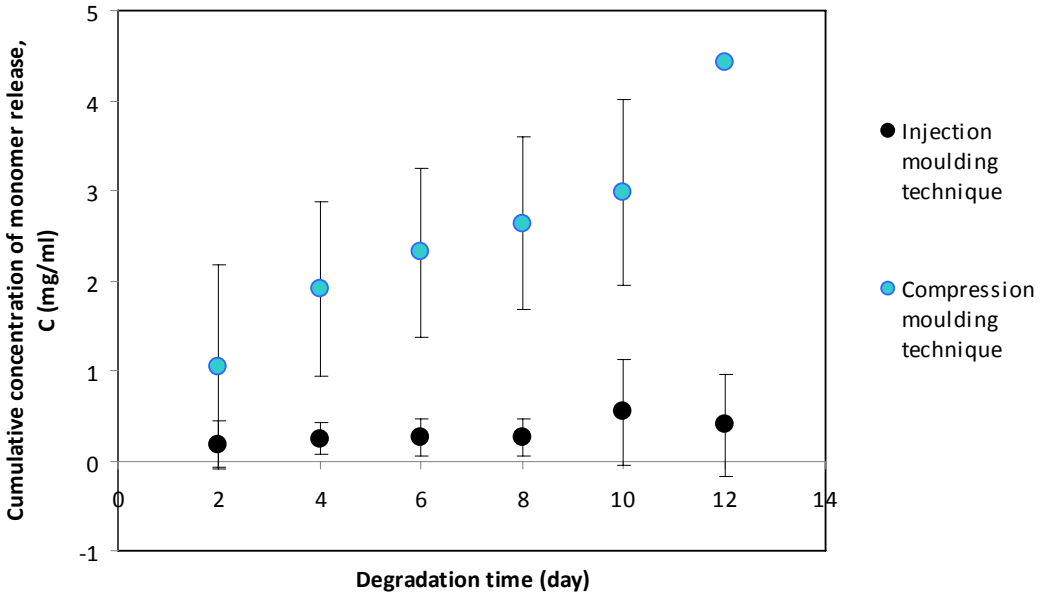


Fig.7: Monomer release in degradation medium of poly (CPP-co-SA) (20:80) as a function of time (n=3).

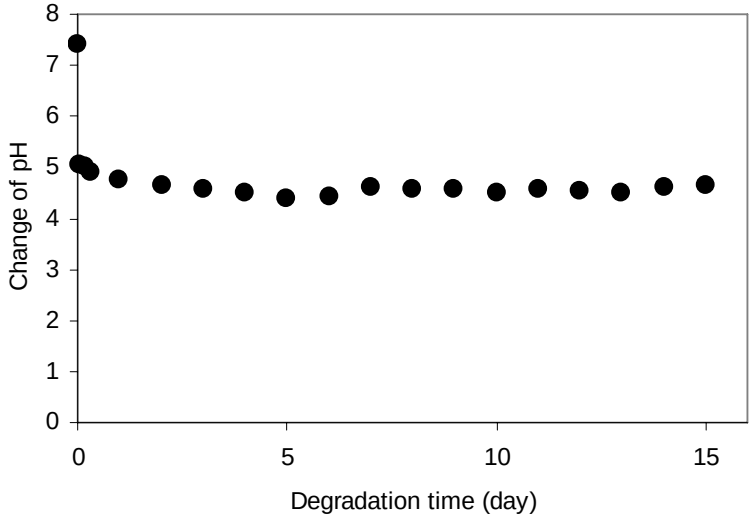


Fig. 8: pH changes as a function of degradation time for poly(sebacic acid) microspheres (n=3).

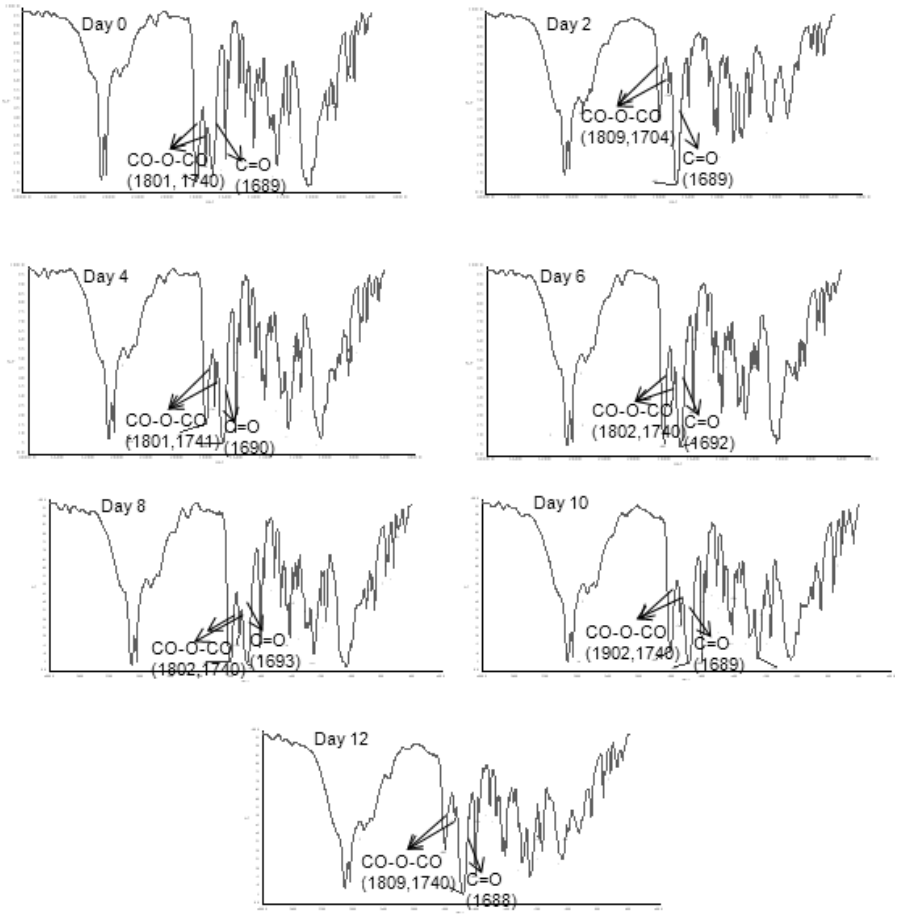


Fig. 9: Evolution of anhydride (1810 cm^{-1} and 1746 cm^{-1}) and carbonyl (1695 cm^{-1}) peaks from FTIR spectra of rod samples throughout the degradation period.

On the other hand, a drastic drop of pH from 7.4 to about 4.8 on the first day was observed for poly(sebacic acid) microsphere (Fig. 8) which correlated well with the drastic mass loss on similar period of time. This suggested a rapid degradation of the microspheres once in contact with the degradation medium. The pH was quite constant at 4.8 throughout the degradation period.

Chemical changes through Fourier Transform Infra Red Spectra

Fig.9 revealed the FTIR spectrum of the degrading injection moulded samples in which the existence of the anhydride peak was found to decrease with degradation time. The COO^- peak which corresponds to the carboxylic group of the acidic monomers increased with degradation time. Even before the samples were in contact with water, the COO^- peak has already appeared in the spectrum. This indicated the early degradation of the samples which could possibly be due to the unavoidable handling problems which failed to minimize the contact with moisture. It was worth noting that the COOCO peak prevailed even at day 12.

Comparing this result with that of the cold compression moulded samples (Fig. 10), similar trend of decrement and increment of COOCO and COO^- respectively was observed. The only difference that can be noted was the early disappearance of the anhydride (COOCO) peak starting from day 8 onwards, whilst this was not featured in the FTIR spectrum of the injection moulded samples. Early degradation of the samples was not visible in the spectrum. These results supported the fact that injection moulded samples exhibited a slower degradation rate when compared with the samples prepared from the compression moulding technique.

The FTIR spectra (Fig. 11) for blank microspheres did not show any changes throughout the degradation period. Anhydride (COOCO) peak at 1810 cm^{-1} remained almost at similar intensity which was quite unexpected as we would have thought that as degradation proceeded with time, the anhydride peaks should be decreasing. The anhydride bonds are indication of the existence of the polymerization of sebacic acid monomers into poly (sebacic acid). As water molecules cleaved the anhydride bond, degradation of the polymer backbone took place and resulted in loss of the monomers into the degradation medium. The amount of poly (sebacic acid) would be reduced and the sebacic acid monomers increased. Interestingly, the COO^- peak at 1700 cm^{-1} which referred to the sebacic acid monomers appeared as early as day 0 and this indicated that early degradation had commenced even when not in contact with the degradation medium.

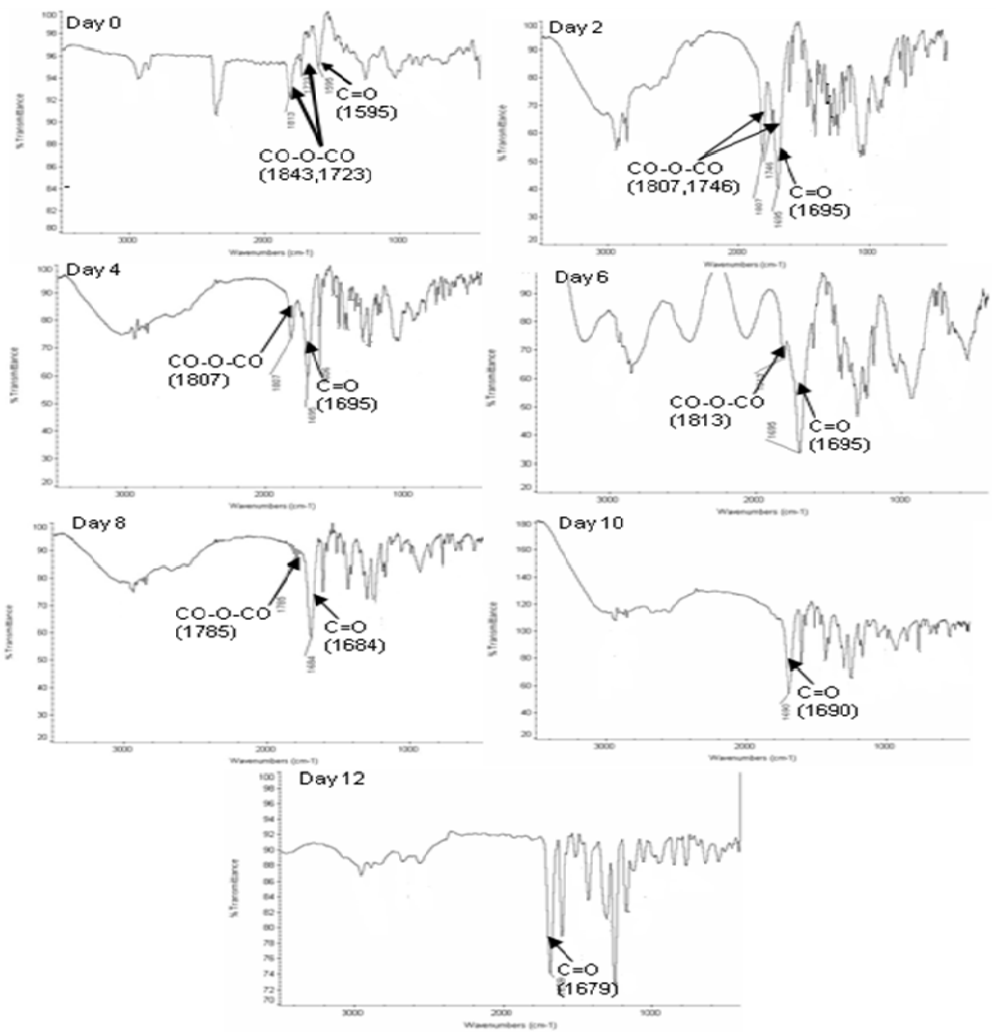


Fig. 10: Evolution of anhydride (1810 cm^{-1} and 1746 cm^{-1}) and carbonyl (1695 cm^{-1}) peaks from FTIR spectra of disc samples throughout the degradation period.

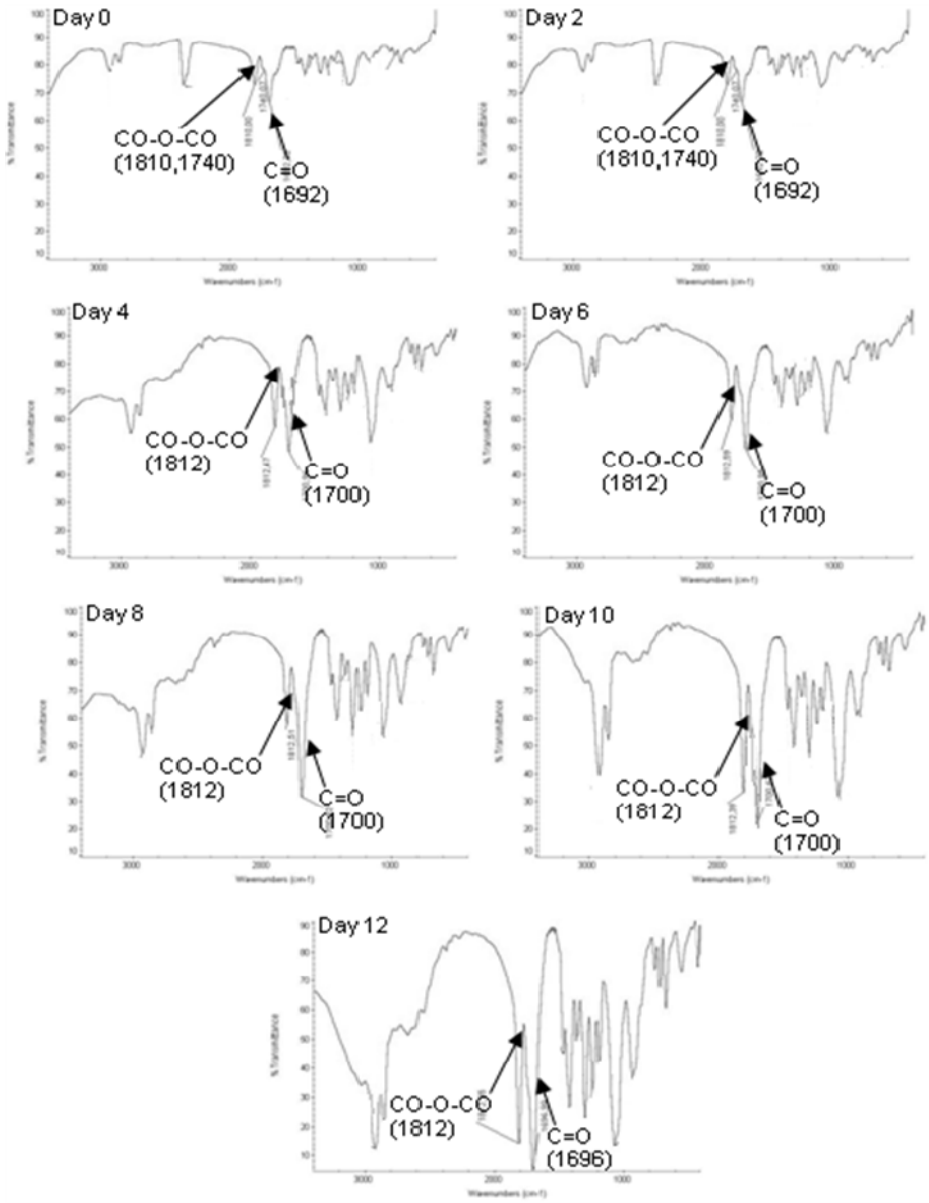


Fig. 11: Evolution of anhydride (1810 cm^{-1} and 1746 cm^{-1}) and carbonyl (1695 cm^{-1}) peaks from FTIR spectra of poly (sebacic acid) microcapsules throughout the degradation period.

Crystallinity

Crystallinity plays a major role in determining the degradation rate of a polymer. Polymers with high percentage of crystallinity normally experience a slow rate of degradation due to the difficulty of water penetration into the polymer bulk. The amorphous part of the polymer will be first removed once degradation ensues and this will be slowly followed by the hard crystalline portion of the polymer.

Fig. 12 shows the comparison of the evolution of the percentage of crystallinity between the disc and rod samples. The percentage crystallinity of the disc samples was 20 % higher than that of the rod samples on day 0 and this could most possibly due to the rapid cooling in the injection moulding process. The injection moulding applied heat for the polymer to flow and the semicrystalline polymer when in a melt state was normally amorphous. As cooling starts, crystal growth began at the nucleus and crystal formation continued until the temperature of the material dropped to a point where chain mobility inhibited further growth. The rate at which crystallinity developed is highly temperature dependent and referred to as the cooling rate. Slow cooling rate resulted in higher crystallinity, on the other hand, rapid cooling caused a reduction in the crystalline formation as seen in Fig. 12.

The polymer chain cleavage normally resulted in short chain monomers and oligomers. Even though most of the monomers and the oligomers eventually diffused out of the polymer body once they reached their critical molecular weight, some part stayed in the polymer and rearrangement of the remaining oligomers and monomers in an orderly manner formed new crystallite materials. This caused an increase in the percentage of crystallinity of the degraded copolymer as seen in Fig. 12. Both disc and rod samples showed an increase in crystallinity once in contact with the degradation medium and at longer degradation time, a constant value was observed.

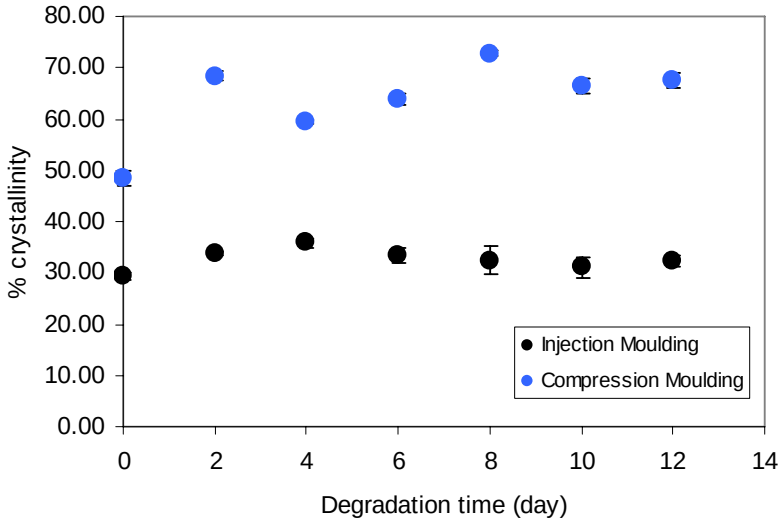


Fig. 12: Percentage of crystallinity poly (CPP-co-SA) (20:80) as a function of degradation time (n=3).

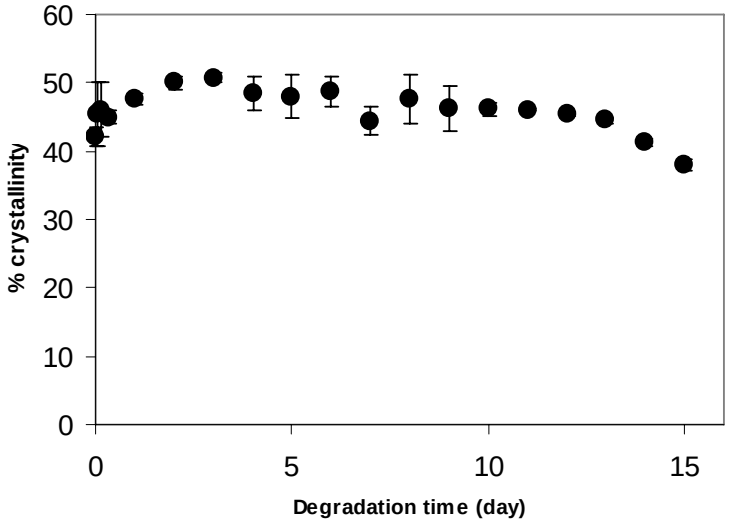


Fig. 13: Percentage of crystallinity of poly (sebacic acid) microspheres as a function of degradation time (n=3).

The percentage crystallinity of the microspheres (Fig. 13) was calculated at 43 % and increased to about 52 % on the first 4 days before being quite stable at 50 % from day 5 to day 8. A slight decrease of about 38 % was demonstrated from day 9 to day 15. Similar explanation could be used to describe the initial increase of crystallinity in the microspheres which normally depicted the loss of amorphous materials and insertion of secondary crystallization.

Thermal studies

Further evidence on the emergence of the monomers during degradation and the increment of the percentage crystallinity could also be observed from the DSC tables. Tables 1 and 2 depicted the copolymer with a melting peak at around 74 °C (T_{m1}) whilst the monomers of sebacic acid and CPP have melting points at 137 °C (T_{m2}) and 322 °C (T_{m3}) respectively. DSC thermograms provided some useful information in relating the rate of the degradation of the copolymer with the appearance and disappearance of the melting peaks of the components in the copolymer. Generally, as the copolymer degraded, its melting peak slowly disappeared from the thermogram accompanied with lowering of the heat of fusion (ΔH_m). The melting peaks of the monomers appeared in the thermogram which depicted the coexistence of the monomers and its copolymer in the polymer bulk.

The compression moulded samples (Table 1) clearly possessed a faster disappearance of the melting peak of the copolymer as early as day 8, 4 days earlier than that of the samples prepared from injection moulding method (Table 2). The early disappearance, pointed to the fact that the compression moulded samples degrade at a faster rate to their respective acidic monomers of sebacic acid and CPP monomers.

The injection moulded samples demonstrated exactly what we had expected for a slower degradation rate (Table 1). Initially on day 0, there was only one melting peak which referred to the copolymer existed in the polymer bulk. Once being degraded, the appearance of the sebacic acid monomer was detected to coexist with the copolymer as early as day 2 and on day 4, the CPP monomer coexisted together with the copolymer and sebacic acid monomer. The coexistence of the three components prolonged until day 10 and on day 12, the melting peak of the copolymer disappeared from the thermogram leaving only the monomers in the polymer bulk.

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

Degraded poly(CPP-co-SA) (20:80)	T_{m1} (°C)	ΔH_{m1} (Jg^{-1})	T_{m2} (°C)	ΔH_{m2} (Jg^{-1})	T_{m3} (°C)	ΔH_{m3} (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

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

Degraded poly(CPP-co-SA) (20:80)	T_{m1} (°C)	ΔH_{m1} (Jg^{-1})	T_{m2} (°C)	ΔH_{m2} (Jg^{-1})	T_{m3} (°C)	ΔH_{m3} (Jg^{-1})
1. Day 0	74	65	-	-	-	-
2. Day 2	81	35	132	85	-	-
3. Day 4	77	22	128	24	265	11
4. Day 6	75	31	131	86	249	11
5. Day 8	73	53	127	11	263	18
6. Day 10	74	40	132	25	261	18
7. Day 12	-	-	138	113	290	39
8. SA Monomer	-	-	137	199	-	-
9. CPP Monomer	-	-	-	-	322	176

Unlike the disc and rod samples, the microspheres of poly (sebacic acid) showed an early degradation based on the existence of the monomer's melting point at day 0. Poly(sebacic acid) had a melting point at about 76 °C (Table 3) whilst the melting point of sebacic acid monomer is at 137 °C. The thermogram at day 0 of blank microspheres showed two melting points at 76 °C (T_{m1}) and 118.59 °C (T_{m2}) and these peaks referred to both poly(sebacic acid) and the sebacic acid monomer respectively. As degradation proceeded, the melting peak of T_{m1} moved slightly to a higher temperature and remained quite stable towards the end of the degradation period. Similar observation was also made for Tm_2 which slightly shifted towards the melting peak of sebacic acid monomer. The heat of fusion for both melting peaks did not show a significant change except for a slight reduction of ΔH_{m1} which might be due to the possible reduction of the degraded poly(sebacic acid). These observations pointed to the fact that not much changes occurred for blank microspheres which correlated well with the FTIR and XRD data.

Table 3: Shifting of melting temperature (T_m) and the heat of fusion (ΔH_m) values for degraded poly (sebacic acid) microspheres as a function of degradation time.

Degraded Blank Microspheres of Poly(sebacic acid)	T_{m1} (°C)	ΔH_{m1} (Jg^{-1})	T_{m2} (°C)	ΔH_{m2} (Jg^{-1})
1. Day 0	76.03	66.17	118.59	64.34
2. 0.04 hrs	76.73	39.75	127.53	151.52
3. 0.16 hrs	76.93	7.98	132.69	150.03
4. 0.32 hrs	77.75	8.74	133.38	163.39
5. Day 1	83.15	36.62	127.94	133.05
6. Day 2	84.16	38.59	126.39	89.19
7. Day 3	85.06	31.01	122.86	97.36
8. Day 4	82.20	94.86	126.42	133.77
9. Day 5	82.87	50.73	132.22	72.01
10. Day 6	85.75	75.97	121.27	81.87
11. Day 7	85.05	62.04	126.44	167.66
12. Day 8	84.53	37.66	128.52	117.81
13. Day 9	86.13	41.22	127.64	90.35
14. Day 10	78.38	52.47	126.07	115.22
15. Day 11	77.48	35.75	128.65	138.53
16. Day 12	78.03	51.87	125.18	123.20
17. Day 13	75.58	43.71	126.67	126.40
18. Day 14	77.82	40.69	127.59	126.81
19. Day 15	78.66	36.03	128.24	119.70
20. SA monomer			137.0	119.0

The degradation data obtained from the EPSEM images, mass loss, water uptake, pH reduction, monomer release, FTIR and DSC gave a good indication of the influence of the method of preparing the samples. Injection moulded samples were thought to have a slower degradation rate when relatively being compared with the samples prepared from the compression moulding method. The morphology distribution and evaluation of the samples prepared from the injection moulding technique was thought to be greatly influenced by the crystallization kinetics in the processing conditions which included high cooling rates and pressures, viscosity and rheology of the polymer. Studies [9] have shown that the polymeric rod samples normally possessed high orientation layer close to the skin which featured the distributions of spherulites radii, crystalinity of α and mesamorphic phases and a decrease of orientation was found towards the central zone. This explained the slightly slower degradation behaviour shown by the rod samples in which water diffused quite slowly into the skin layer of the rod prior to the degradation activity. In contrast, the loosely packed polymer particles from the disc samples allowed a quicker diffusion of water and faster polymer degradation ensues.

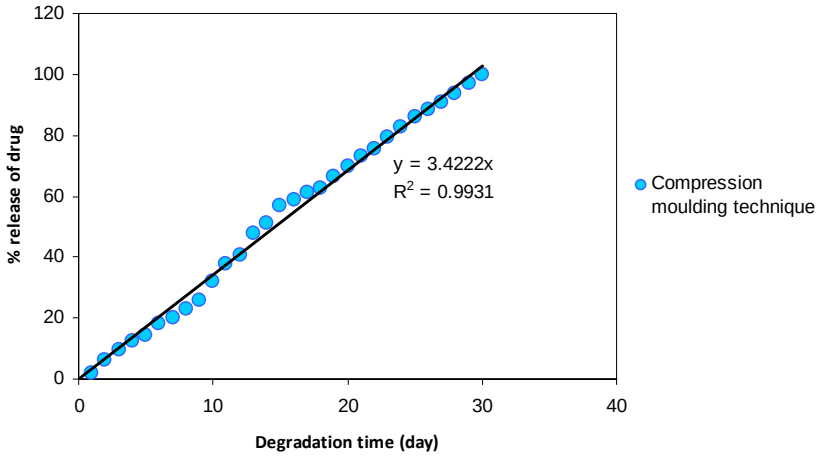
Though other evidence could not have clearly pointed out the erosion mechanism, the EPSEM images however have indirectly suggested the possibility of a surface erosion mechanism. Layers full of cracks were removed and this exposed the new layer underneath. The process was repeated continuously until the samples vanished from the sampling bottle.

In the surface erosion process, the rate of water diffusion into the samples was much slower than the rate of the polymer erosion and degradation. As the erosion front moved from the outermost part of the sample into the internal layer, the drug located on this eroded material will first be diffused out. The release of the drug will be completed once the fronts met at the centre of the samples.

Drug release

Fig. 14 a-b demonstrated the drug release profiles from both samples prepared from injection moulding and compression moulding technique. The release kinetics followed a zero order kinetic release and this was observed for both fabrication techniques. A consistent amount of drug was released throughout the degradation period. Again as expected, injection moulded samples possessed a slower drug release pattern when compared with the release from compression moulded samples. The zero order kinetic is a typical release profile resulting from the surface erosion mechanism. The release profiles also confirmed the hypothetical views of the CPP-SA copolymer of undergoing a surface erosion process.

a)



b)

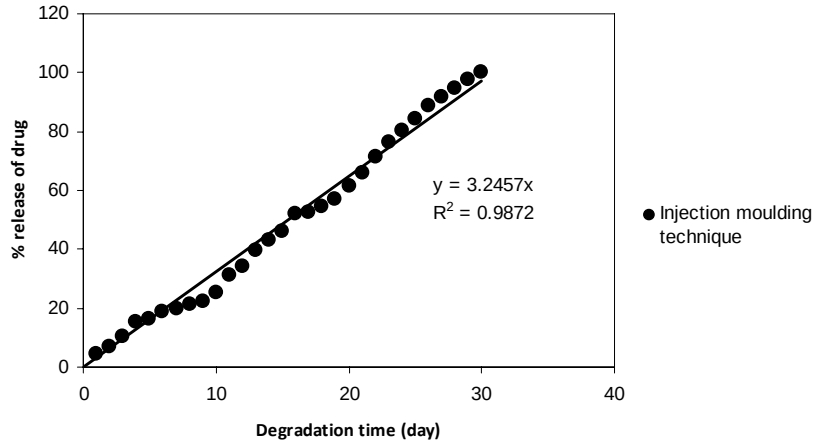


Fig.14: Drug release profile of degraded poly (CPP-co-SA) a) disc samples and b) rod samples following a zero order kinetic release (n=3).

The drug release profile from typical polyanhydride is normally controlled by the surface erosion process. As water diffused into the polymer, the outer most part of the polymer will be first degraded and the drug that was located at the surface of the sample will be released into the degradation's medium. However polyanhydride microspheres exhibited quite a different profile (Fig. 15). A burst release was often observed at the initial stage of the degradation period. The drug incorporation method used in preparing microspheres led to the accumulation of drug on the surface of the microspheres. On top of that, high polymer crystallinity had a strong inclination to push the drug to the outer part of the sample and close to the surface of the microspheres. Once these microspheres were in contact with water, the drug located on the surface was washed off resulting in the high burst release of the drug at the initial stage.

It was interesting to note that the burst release phenomenon was not well expressed in this work. Microspheres prepared from the synthesized poly(sebacic acid) did not demonstrate a high burst release (Fig. 15). Less than 10 % of drug was released on day 1 followed by a steady release of the drug until day 15. The release profile showed a close approximation to the Higuchi release profile based on the Fick's law of square root of time [10] dependent expression as follows:

$$Q_t = K_H t^{1/2} \qquad (3)$$

where Qt is the amount of drug released in time t and K_H is the rate constant for Higuchi equation. The release profile (Fig. 16) was then plotted against $t^{1/2}$, in which a fit straight line was obtained. These results gave a good indication that the drug release profile from poly(sebacic acid) microspheres was affected by several competing factors. First was the polymer erosion process that took place throughout the degradation period. This was quite convincing as the drug located in the amorphous part of the polymer could be released together with the loss of the polymer. The second factor could come from the porous structure of the microsphere as shown in the SEM micrographs. Drug dissolution through the water filled pores could also take place. Third was the drug dissolution from the polymer matrix based on the modified release system as a diffusion process based on Higuchi model. The drug was thought to release via diffusion through the polymer backbone and this was depicted in Fig. 16.

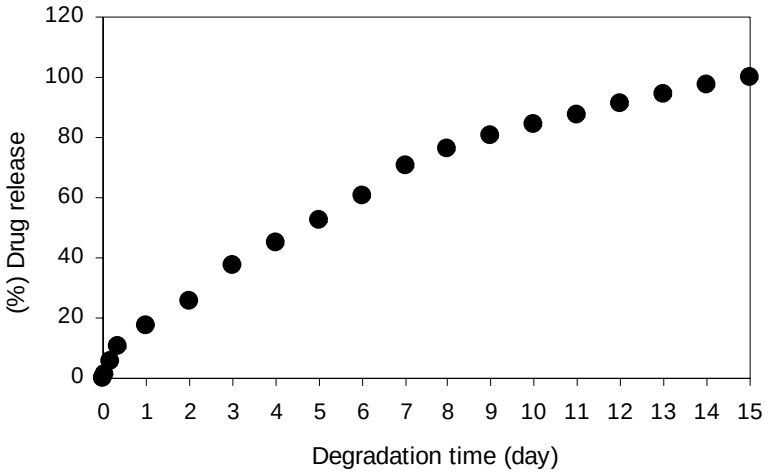


Fig. 15: Drug release profile of poly (sebacic acid) microspheres (n=3).

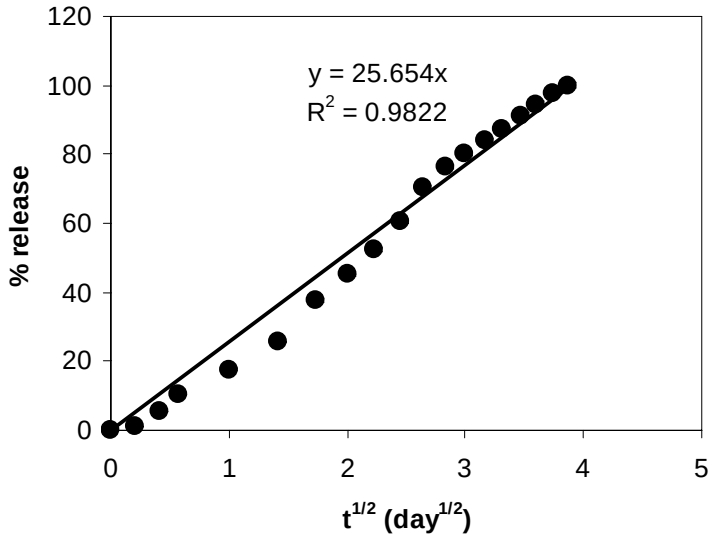


Fig. 16: Drug release profile of poly (sebacic acid) microspheres at $t^{1/2}$ $(day)^{1/2}$

CONCLUSION

The fabrication technique imposed in this work showed some influence on the degradation and drug release characteristic of polyanhydride. Rod samples from injection moulding technique exhibited a slower degradation and drug release behaviour compared with discs samples prepared from the cold compression moulding. This was highly due to the evolution of the polymer morphology during processing. Drug release was mainly controlled by surface polymer erosion. Poly (sebacic acid) microspheres on the other hand, showed a faster degradation rate with burst drug release pattern following the square root of time profile.

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