Experimental Approach To Elucidate the Mechanism of Ultrasound-Enhanced Polymer Erosion and Release of Incorporated Substances

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ABSTRACT: Studies were conducted on the mechanism of ultrasound-enhanced solid polymer degradation in the presence of a liquid. Polyanhydride degradation and release experiments were performed at different temperatures. Considering that the change of temperature affects degradation product solubility, solution gas content, and vapor pressure, the dependence of ultrasound-enhanced degradation on the above three factors was investigated. The role of free radicals produced by ultrasound and the effect of ultrasound on hydrolysis versus mechanical erosion were also investigated using a nonaqueous solvent as the liquid phase. The results suggest that ultrasound accelerates both polymer hydrolysis and mechanical surface erosion. These effects might be explained by enhanced transport (enhanced permeation of water into the polymer exposing more hydrolytically labile linkages for hydrolysis) and mechanical shear stress mainly caused by the liquid jets at high velocity produced when the gas bubbles collapse (cavitation). The rate of ultrasound-enhanced polymer degradation increases with increasing liquid vapor pressure. These two parameters control the extent of cavitation.

Introduction

The approach of using ultrasound to enhance the drug delivery rate from solid biodegradable polymers, such as polyanhydrides, might produce a useful way of externally regulating release rates from polymers in a variety of situations where on-demand release is required without adding any additional substances (e.g., enzyme, magnetic beads) to the polymer matrix. Studies on ultrasound-enhanced polyanhydride degradation and the release of incorporated substances with high- and low-intensity ultrasound have been performed,[1,2] which established that cavitation is an important part of the mechanism by which ultrasound effects degradation. In the present study, the effect of physicochemical factors such as temperature, solution gas content, radicals produced by irradiation with ultrasound, and solution vapor pressure on the ultrasound-enhanced polymer erosion and the release of incorporated substances was investigated. The mechanism of ultrasound-enhanced polymer degradation was also studied.

Experimental Section

All chemicals were reagent grade. Potassium iodide, *tert*-butyl alcohol, dimethyl sulfoxide (DMSO, packed under nitrogen in Sure/Seal bottles, H_2O content <0.005%), and *p*-nitroaniline (PNA) were from Aldrich Chemical Co. Poly(lactic acid) (PLA, M_w = 50 000) was from Polyscience Inc., and 1,3-bis(*p*-carboxyphenoxy)propane (CPP) monomer was a gift from Nova Pharmaceuticals Corp. Copolymers of CPP and sebacic acid (SA) [P(CPP/SA)] (CPP:SA = 20:80 and 50:50) as well as poly[1,6-bis(*p*-carboxyphenoxy)hexane] [P(CPH)] were synthesized as described previously.[3] The weight-average molecular weights (M_w) were 32 000, 21 000, and 29 000 for P(CPP/SA)(20:80), P(CPP/SA)(50:50), and P(CPH), respectively, as analyzed by gel permeation chromatography (GPC) on a Perkin-Elmer instrument (Perkin Elmer Corp., Model series 10) equipped with a multiple-wavelength UV detector (LKB-2140), using polystyrene as a standard in chloroform solution.[4]

For PNA release studies, the devices containing PNA were prepared as follows:[1,2] For PNA-loaded P(CPP/SA) and P(CPH), the polymer was ground in a Micro Mill Grinder (TechniLab Instruments Inc., Model 502) at a speed of 12 000 rpm, sieved into particles with a size range of 9–150 μm, and then mixed manually in an alumina mortar and pestle (Scientific Products) with PNA which was ground (Micro Mill Grinder, TechniLab Instruments, Model H37252) and sieved to the same size range. The mixture (about 0.1 g) was placed into a mold of cylindrical shape (8 mm in diameter) and compression molded in a Standard PanaVise (Ladd Research Industries, Inc., Model 6-11492) at room temperature, followed by 15 min in an oven maintained at 80 °C under pressure. The final thickness of the device was about 1 mm. For PNA-loaded poly(lactic acid), the poly(lactic acid) and PNA were dissolved in chloroform. Following film casting at room temperature, the PNA-loaded films were then ground, sieved, and compression molded as described above. In all cases, the weight ratio of PNA to polymer in the devices was 10%. For the polymer erosion investigations, the devices were made from sieved powder of P(CPP/SA)(20:80), P(CPP/SA)(50:50), and P(CPH) without PNA using the same method as above.

For in vitro erosion studies the device was preincubated in 50 mL of pH 7.4 phosphate buffer (PB) at 37 °C for 18 h, so that the erosion experiments were performed after the period of the initial lag phase of erosion.[2] The device was then placed into a jacketed cell containing 50 mL of PB, which was maintained at a constant temperature by circulating water through the jacket. The ultrasound probe at a frequency of 1 MHz and an intensity of approximately 1.7 W/cm² (Enraf-Nonius, Sonopuls 434, Holland) was placed in position in the jacketed cell.

Polymer erosion was detected continuously by circulating the PB at the rate of 14.0 mL/min through a UV spectrophotometer (Beckman Instrument Inc., Model DU 65), using a peristaltic pump (Rainin Instrument Co., Inc., Rabbit-Plus). CPP accumulation was detected at 246 nm and PNA at 381 nm.

To ensure that the CPP dissolution kinetics is not the limiting step that affects the CPP appearance in the solutions, several experiments were performed in which the P(CPP/SA) device was taken out of the jacketed cell after exposure to ultrasound at 298 K for 2 h and the optical density (OD) was followed for

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24 h. No change in the OD of the PB solution was observed, suggesting that no undissolved CPP was present.

The erosion rate and the release rate of PNA were calculated from the slopes of plots of CPP accumulation or released PNA vs time, respectively. The activation energies of polymer erosion were calculated according to the Arrhenius equation by plotting reaction constant as a function of inverse temperature (ln k vs $1/T$).

To determine the effect of temperature on the erosion of copolymers and the release of incorporated substances, experiments were performed at 283, 298, 313, and 328 K. PB was placed into a biochemical oxygen demand (BOD) bottle (Thomas Scientific, Model 1781-N23), into which air was bubbled at the specified temperature until the dissolved air content did not change by measuring oxygen content using an oxygen electrode (Orion Research Inc., Model 970800), utilizing a dual scheme of thermocompensation.

To determine the effect of gas content on the erosion of the copolymers, experiments were performed at a fixed temperature in a series of PB solutions containing different oxygen concentrations. The PB solutions with different oxygen contents were prepared by sparging oxygen (pressure: 100 kPa) into degassed PB solution for different time intervals, followed by oxygen measurement.

To investigate the role of free radicals produced by irradiation of ultrasound during the erosion of polymers and the release of incorporated drugs, radical scavengers such as potassium iodide and *tert*-butyl alcohol were added. The competition of the scavengers for the free radicals was detected at 350 nm following the appearance of I_2 after the addition of 0.1 M KI and several concentrations of *tert*-butyl alcohol. In experiments following CPP accumulation, 1 mL of 0.01 M Na_2SO_3 was added 20 min before the OD measurement (Na_2SO_3 decreases the concentration of iodine, which interferes with CPP detection).

The solubility of CPP and PNA was measured as follows: 1.0 g of CPP or PNA powder was placed into a 10-mL solution containing different concentrations of PB/*tert*-butyl alcohol or PB/DMSO at different temperatures. The amount of dissolved CPP or PNA was determined by measuring the OD of the filtered solution, as described above, at intervals of 2 h until the change of OD between consecutive measurements was below 0.005.

Results

Temperature Effect. Erosion and release experiments were first performed at different temperatures using both drug-free and PNA-loaded devices made of P(CPP/SA)-(20:80), P(CPP/SA)(50:50), P(CPH), and PLA, either exposed or not exposed to ultrasound. At a given temperature the erosion rate of P(CPP/SA) and/or the release rate of PNA was significantly enhanced when exposed to ultrasound (Figures 1 and 2), supporting previous publications.[1,2] The erosion and release rates increased with increasing temperature in each experiment with or without ultrasound (Figures 3 and 4). In all cases the devices display near-zero-order erosion and release rates within the 2 h examined. The zero-order behavior was unaltered either by the change of temperature or by the exposure to ultrasound.

Considering that the change of temperature brings about (1) different solubilities of polymer degradation products, (2) different solution gas contents, and (3) different solution vapor pressures, the dependence of ultrasound-induced polymer degradation on the above three factors was investigated.

The solubility of CPP monomer and PNA in PB at different temperatures was measured (Figure 5). Similar to the temperature dependence of polymer erosion and PNA release, the solubility of CPP and PNA increases with temperature (Figures 3–5) and became much higher at 328 K than at 283 K.

Solution gas contents have been demonstrated to be an important factor in ultrasound-induced degradation of

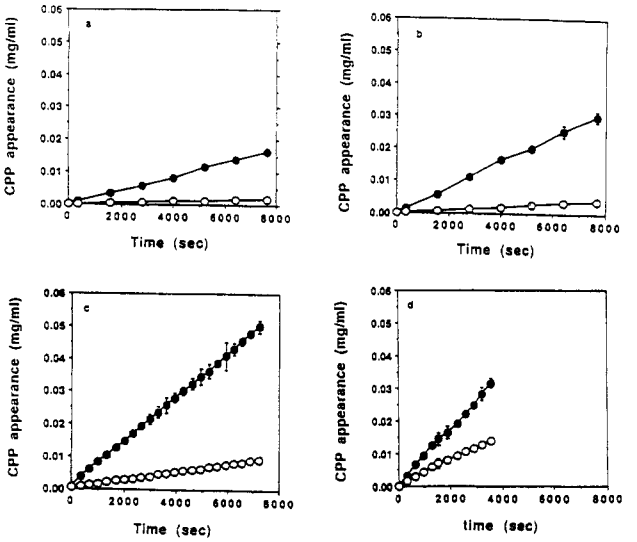

Figure 1. Effect of temperature on the in vitro polymer erosion at (a) 283, (b) 298, (c) 313, and (d) 328 K with exposure to ultrasound (●) and without ultrasound (○).

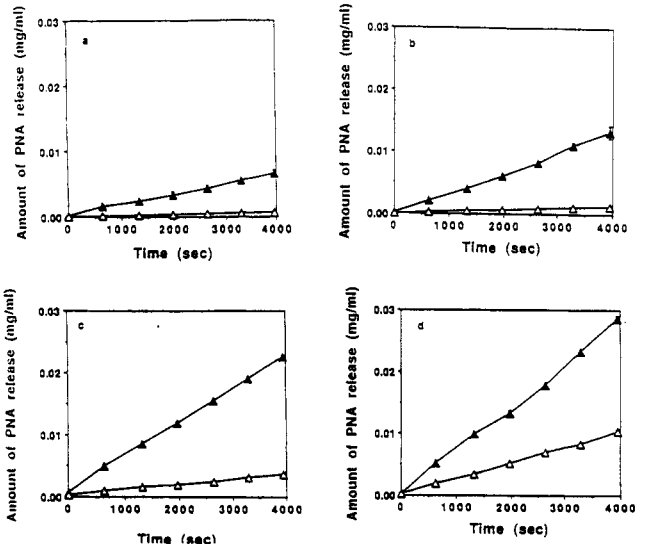

Figure 2. Effect of temperature on the release of incorporated PNA at (a) 283, (b) 298, (c) 313, and (d) 328 K with exposure to ultrasound (▲) and without ultrasound (△).

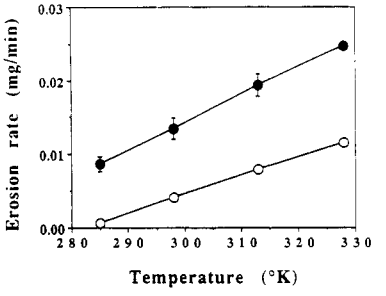

Figure 3. Temperature curve of the erosion rate of P(CPP/SA)(20:80) with ultrasound (●) and without ultrasound (○).

soluble polymers, such as polynitrobenzene and polystyrene.[5,6] Since in the above experiments, the solution gas content decreases with increasing temperature, the following experiments were performed at a fixed air content at different temperatures. As shown in Figure 6 the erosion rate of P(CPP/SA)(20:80) was promoted by an increase of temperature at any given air content.

Erosion experiments of P(CPH) also show an increase of erosion rate with increasing temperature at a fixed

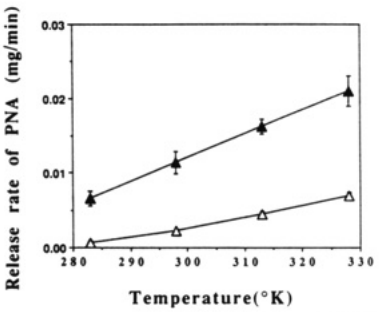

Figure 4. Temperature curve of PNA from P(CPP/SA)(20:80) with exposure to ultrasound (▲) and without ultrasound (△).

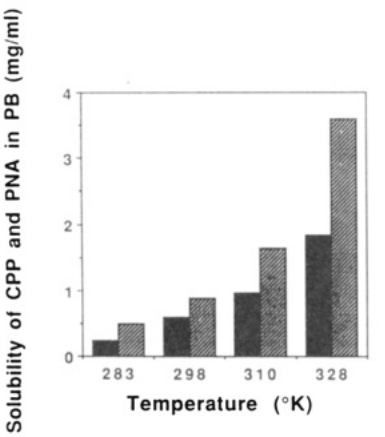

Figure 5. Solublity of CPP (black bars) and PNA (hatched bars) in PB at different temperatures.

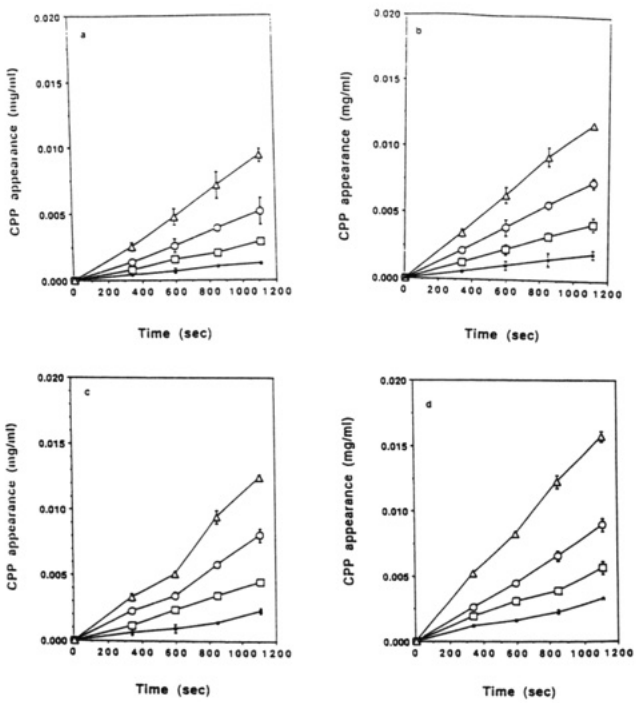

Figure 6. Effect of air content on in vitro polymer erosion at different temperatures (△, 328 K; ○, 313 K; □, 298 K; ■, 283 K) with exposure to ultrasound. The air content dissolved in PB solutions as detected by dissolved oxygen content is (a) 6.02, (b) 7.52, (c) 9.15, and (d) 11.2 ppm.

solution air content (Figure 7). A similar relationship between the release rate of incorporated PNA and reaction temperature was also found at two different solution air contents (Figure 8).

Solution Gas Content Effect. It was also shown (Figures 6–8) that the erosion rate of the polymer and the

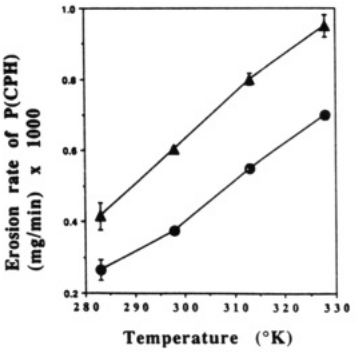

Figure 7. Temperature curve of the erosion rate of P(CPH) with exposure to ultrasound at two different solution air contents. The air content dissolved in PB solutions as detected by dissolved oxygen content is (▲) 11.2 and (●) 7.52 ppm.

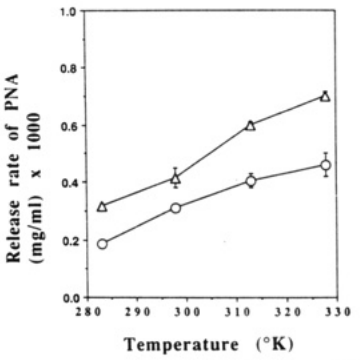

Figure 8. Temperature curve of PNA released from P(CPH) devices at two different solution air contents with exposure to ultrasound. The oxygen concentration in the dissolved air is (△) 11.2 and (○) 7.52 ppm.

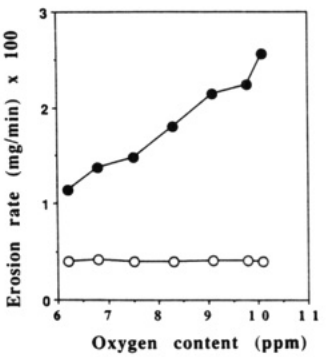

Figure 9. Effect of solution oxygen content on the erosion rate of P(CPP/SA) with exposure to ultrasound (●) and without ultrasound (○) at 298 K.

release rate of the incorporated PNA increased with the air content at a given temperature. To evaluate the importance of solution gas content on the ultrasound-enhanced polymer degradation, the erosion rate of polyanhydrides was further investigated using drug-free P(CPP/SA)(20:80) placed in PB solutions containing pure oxygen at different concentrations at a given temperature, in experiments with and without exposure to ultrasound. As can be seen (Figure 9) oxygen content has an effect on the erosion rate only when the polymer is exposed to ultrasound.

Figure 10 displays the isothermal curves of the PNA released from P(CPP/SA)(20:80)/PNA (a) and PLA/PNA (b) at different oxygen contents. In experiments where samples were not exposed to ultrasound, the release rate of PNA increased only with an increase of temperature and was independent of oxygen content. In experiments in which the samples were exposed to ultrasound, PNA

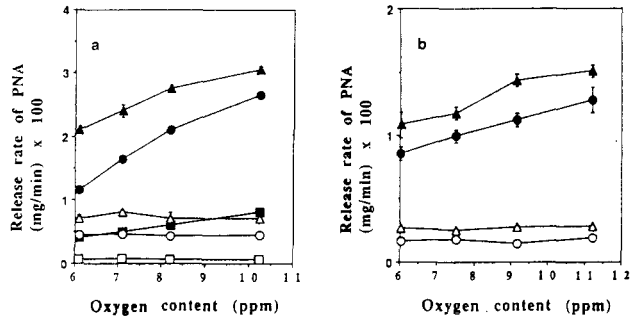

Figure 10. Isothermal curves of PNA released from (a) P(CPP/SA)(20:80) and (b) PLA devices (■); 298 K and exposure to ultrasound; (□) 298 K without ultrasound; (●) 313 K and exposure to ultrasound; (○) 313 K without ultrasound; (▲) 328 K and exposure to ultrasound; (△) 328 K without ultrasound.

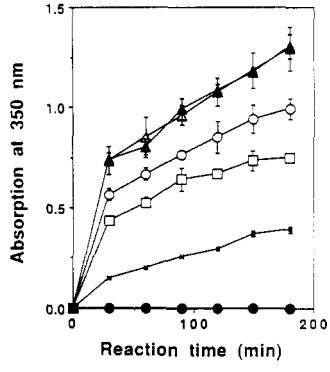

Figure 11. Iodine yield as a function of the KI concentration in PB irradiated by ultrasound at 295 K. KI concentration was (×) 0.05, (□) 0.1, (○) 0.5, (△) 1.0, and (▲) 2.0 M. 1.0 M KI (●) without ultrasound irradiation was used as a control.

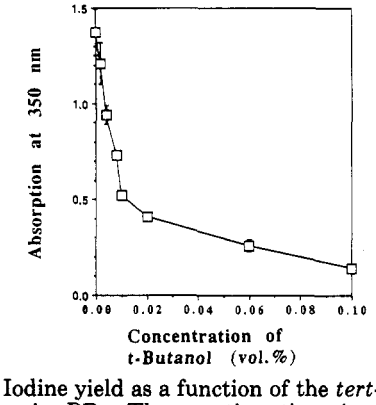

Figure 12. Iodine yield as a function of the *tert*-butyl alcohol concentration in PB. The reaction time is 180 min, the concentration of KI is 1.0 M, and the reaction temperature is 298 K.

release rate increased in proportion to oxygen content in the PB solution, at the same temperature.

The Role of Radicals. The time curve of I_2 produced by ultrasound irradiation is shown in Figure 11. The rate of I_2 production increases with KI concentration; however, when KI concentration was over 1 M, the rate of I_2 production was not changed further. Addition of *tert*-butyl alcohol to 1.0 M KI decreased the I_2 production when the solution was irradiated with ultrasound (Figure 12).

Experimental results of the effects of radical scavenger (KI and *tert*-butyl alcohol) on the erosion of P(CPP/SA) are shown in Figure 13. As can be seen the addition of KI did not affect the CPP appearance while the addition of *tert*-butyl alcohol decreased the CPP appearance.

The Effect of Nonaqueous Solvent. Solubilities of CPP in a solution of PB and in an organic solvent such

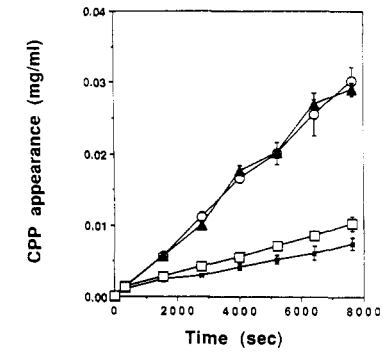

Figure 13. Time curve of P(CPP/SA)(20:80) erosion in the presence and absence of radical scavengers at 298 K. The concentration of free-radical scavengers is (×) 0.0001 M *tert*-butyl alcohol, (□) 0.0002 M *tert*-butyl alcohol, and (▲) 1.0 M KI; (○) without radical scavenger.

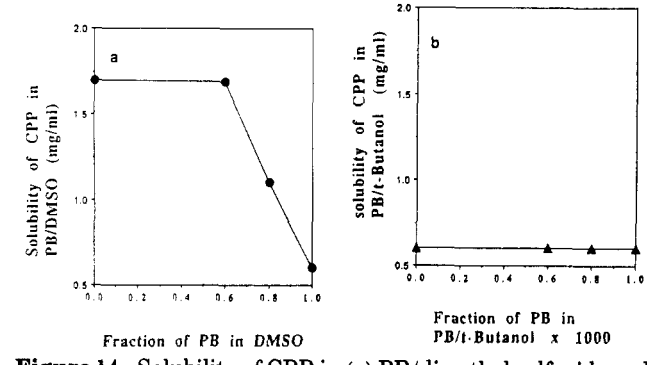

Figure 14. Solubility of CPP in (a) PB/dimethyl sulfoxide and (b) PB/*tert*-butyl alcohol solutions with different volume ratios at 298 K.

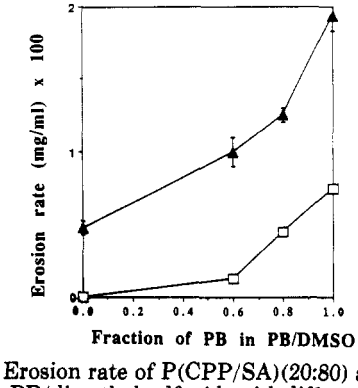

Figure 15. Erosion rate of P(CPP/SA)(20:80) as a function of water ratio in PB/dimethyl sulfoxide with different volume ratios: (□) without exposure to ultrasound; (▲) with exposure to ultrasound. The reaction temperature is 313 K.

as *tert*-butyl alcohol and DMSO were measured (Figure 14). CPP solubility was not affected by the addition of *tert*-butyl alcohol, while the addition of DMSO strongly affected CPP solubility.

The erosion rate of P(CPP/SA) in different DMSO/PB volume ratio solutions with and without exposure to ultrasound is shown in Figure 15. No CPP appearance was found after the device was placed in pure DMSO for 1 h without exposure to ultrasound. When exposed to ultrasound for 1 h in pure DMSO, an erosion rate of 0.001 mg mL^{-1} min^{-1} (10 times higher than the standard deviation, Figure 15) was detected (experiments were performed under nitrogen in DMSO with a water content lower than 0.005%).

Discussion

As can be seen in Figures 1 and 2 the erosion and drug release display zero-order kinetics, suggesting that only

Table I
Ratio of Reaction Rate (k/k')[a] of Erosion of P(CPP/SA) between Subjection to and No Subjection to Ultrasound

	283 K	298 K	313 K	328 K
solution vapor pressure,[b] mmHg	9.21	23.7	55.3	118.0
sample				
P(CPP/SA)(20:80)	10.1	8.3	4.2	2.1
P(CPP/SA)(50:50)	10.4	8.7	4.1	2.4
P(CPH)	9.6	8.1	4.2	2.3

[a] k = reaction rate of the erosion of P(CPP/SA) with exposure to ultrasound; k' = reaction rate of the erosion of P(CPP/SA) without exposure to ultrasound. [b] Data from: Handbook of Chemistry and Physics, 63rd ed.; CRC Press: Boca Raton, FL, 1982–1983; p D-197.

surface erosion is occurring at these temperatures and within the 2-h period even during exposure to ultrasound.

The increase in erosion rate and drug release rate with temperature (Figures 3 and 4) could be due to the fact that the solubility of CPP and PNA changes with temperature. A previous study[8] revealed that the overall polymer erosion was due to several steps, i.e., water diffusion to the labile bond, hydrolysis, and diffusion and dissolution of degraded products. Obviously, all steps could be promoted by an increase of temperature, and the solubility of degradation products might play an important role in determining the erosion rate of polyanhydrides.

The temperature dependence of the solubility of CPP monomer or PNA in PB (Figure 5) is an important factor which might affect the copolymer erosion rate and the release rate of the incorporated drug.[8] However, as shown in previous experiments,[1] in which the erosion and release experiments were performed under vigorous mixing and a higher temperature, the temperature or mixing effect could not explain why the erosion rate of polyanhydride or the release rate of PNA is higher when exposed to ultrasound than without ultrasound.

A different mechanism, cavitation and acoustic streaming, has been suggested as a primary cause of ultrasound-enhanced erosion of solid polymer surfaces.[1] The kinetics and mechanism of ultrasonic degradation of polymers in solution have been extensively investigated.[9-12] The process is thought to be composed of a series of steps: nucleation or formation of cavitation in liquid, bubble growth in an irradiated liquid, and, under proper conditions, implosive collapse. At the stage of the collapse of the cavity, radiated friction forces and shock waves generate the stresses on the surface of a polymer chain and/or more possibly within the polymer coil, resulting in bond breaking of the macromolecular chain in the liquid, which is similar to hydrodynamic shear degradation.[13,14] In the process of shear macromolecular degradation, radicals are also formed, accelerating the depolymerization. It has also been demonstrated that some physicochemical factors, such as solution vapor pressure, temperature, radical yield, and solution gas content, are important variables[5,15] for the degradation of polymers in solution. These factors could affect cavitation formation and cavitation collapse, resulting in a different rate of polymer degradation and/or different degradation products. While the effect of ultrasound on polymers in solutions has been studied, there have been just a few previous examinations of ultrasound on liquid–solid systems[12] and almost no reports on liquid–solid polymer systems.[1] In the present study, the role of factors which affect the ultrasound-enhanced polymer solution degradation and liquid–solid system was investigated. The first experiments were conducted to characterize the cavitation effect, which is known to be dependent on vapor pressure and gas content.[15,16]

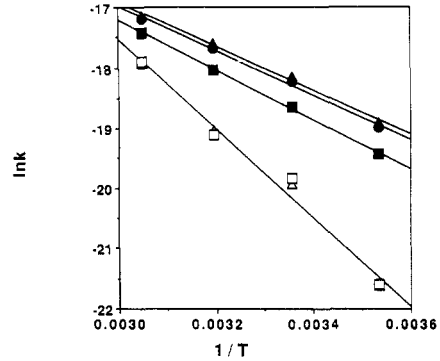

Figure 16. Plot of ln k vs $1/T$: (■,●,▲) with exposure to ultrasound; (□,△) without ultrasound. The oxygen concentration of dissolved air in PB is (■,□) 7.52, and (▲,△) 11.2 ppm.

For polymer solutions, the rate of cavitation-induced reactions decreases with increases in the solution vapor pressure. For example, when a higher vapor pressure compound such as ethanol is added to nitrobenzene, the polymerization rate initiated by cavitation bubble collapse decreases.[15] A similar relation between the solution vapor pressure and erosion rate for ultrasound-enhanced liquid–solid polymer degradation was found, suggesting a similar mechanism. The vapor pressure was controlled by temperature (Table I) or solution composition (Figure 13). In polymer solutions it was thought that the decreased cavitation effect was due to the fact that bubble collapse was partially buffered by the higher solution vapor pressure, resulting in a smaller shock wave damage, minimizing the microjet impact.

The erosion rate of the polymers as well as the release rate of incorporated drugs increased with solution gas content (Figures 6–10). In polymer solutions, similar behavior is attributed to an increased number of nucleation centers which increases with solution gas content, causing increased cavitation density.[6,15] The erosion rate of PCPP/SA copolymers either exposed or not exposed to ultrasound displayed Arrhenius behavior (Figure 16). The activation energies at different gas contents which were calculated based on these results are presented in Table II. The activation energy is not dependent on gas content as long as the polymers were not exposed to ultrasound, while the activation energy decreases with gas content for the exposed samples, indicating again the importance of the cavitation mechanism.

The hypothesis that ultrasound affects the release and degradation kinetics as a result of radical formation was evaluated. It was reported that iodine can be produced by ultrasound irradiation of aqueous KI.[7] Therefore the appearance of iodine suggests production of radicals in solution (KI and *tert*-butyl alcohol) are known radical scavengers.[7,15]

$$I^- + R^\bullet \rightarrow I_2$$

As can be seen in Figure 11, without ultrasound exposure no radicals were generated in solution while, when exposed to ultrasound, radicals were produced. No effect of KI concentration on I_2 production was observed for concentrations higher than 1 M KI, suggesting that at this concentration all the radicals were scavenged. When *tert*-butyl alcohol was added to the KI solution and exposed to ultrasound, a decrease in iodine concentration was observed due to the competitive reaction of *tert*-butyl alcohol with free radicals (Figure 12).

To evaluate the effect of the produced free radicals on the polymer erosion mechanism, polymer erosion was

Table II
Activation Energy of the Erosion of P(CPP/SA)

gas concn, $cm^3/1000\ cm^3$			act. energy, (J K)/mol	
in water				
air[a]	oxygen, ppm	in PB oxygen, ppm	with ultrasound	without ultrasound
22.84	11.3	11.2	26.52	61.61
17.08	9.08	9.15	30.97	
	7.60	7.52	34.96	61.43

[a] Data from: Handbook of Chemistry and Physics, 70th ed.; CRC Press: Boca Raton, FL, 1989–1990; p B-457.

followed at decreased free-radical concentrations (Figure 13). No effect of decreased free-radical concentration on CPP accumulation was observed when the scavenger used was KI while a significant difference was observed when *tert*-butyl alcohol was added. Despite the scavenging effect of *tert*-butyl alcohol, the decrease in CPP appearance when *tert*-butyl alcohol was added might be due to the high vapor pressure of *tert*-butyl alcohol/PB solution which spoils the bubble collapse,[7] while KI can only scavenge free radicals. These results revealed that the enhanced degradation by ultrasound cannot be attributed to free-radical interactions, while in polymer solutions the effect of free radicals is important.[14,17]

To examine the contribution of ultrasound to each of the separate steps involved in polymer degradation (water diffusion to the labile bond, hydrolysis, diffusion, and dissolution of the degraded products), kinetic experiments were performed in pure DMSO where hydrolysis is impossible and polymer degradation is due to mechanical erosion. Figure 15 demonstrates a significant enhancing effect of polymer erosion by ultrasound in pure DMSO, suggesting that the effect of ultrasound was not attributed just to hydrolysis.

On the basis of the present experiments, it is proposed that the ultrasound-enhanced polymer degradation and release of incorporated substances are based on hydrolysis, mechanical stress, and the cooperation of both factors. Some physicochemical factors, such as solution gas content and solution vapor pressure, do not affect the hydrolysis of the polymer directly but strongly alter the cavitation density and cavitation intensity and, consequently, the erosion rate of polymer and the release rate of incorporated drug.

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References and Notes

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