Preparation, Characterization and *In Vitro* Drug Release Properties of Polytrimethylene Carbonate/Polyadipic Anhydride Blend Microspheres

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ABSTRACT: Polyadipic anhydride (PAA), an aliphatic polyanhydride, and polytrimethylene carbonate (PTMC), an aliphatic polycarbonate, were synthesized via ring opening polymerization of oxepan-2,7-dione and melt-condensation of trimethylene carbonate (1,3 dioxan-2-one), respectively. PTMC–PAA blend microspheres containing different ratios of buprenorphine HCl (2, 5, and 10%) were prepared by an oil-in-oil emulsion solvent removal method. Microspheres with different ratios of PTMC–PAA (85/15, 70/30, and 55/45) containing 5% buprenorphine HCl were prepared. Microspheres were spherical with visible cracks and pores on the surface. The average particle size of microspheres was around 200 μm for all microspheres. Drug loading efficiency of PTMC–PAA microspheres (85/15, 70/30, and 55/45) was 97.2, 95.2, and 70.2%, respectively. With the increase in the PTMC ratio, the melting point and the enthalpy of melting were both decreased. The mechanism for drug release from PTMC–PAA blend microspheres were generally a combination of drug diffusion through polymers and biodegradation of the polymers. In first three days, the release from microspheres followed zero order kinetics and was dependent on the PAA content. After three days the drug release from microspheres followed first order kinetics. In conclusion it was demonstrated that buprenorphine HCl release from microspheres could be successfully controlled by using different ratios of PTMC–PAA blends. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 101: 2377–2383, 2006

Key words: biodegradable polymers; microspheres; buprenorphine HCl; polytrimethylene carbonate; polyadipic anhydride

INTRODUCTION

Biodegradable polymers have vigorously been studied as drug delivery devices[1,2] and in tissue engineering applications[3]. Controlled delivery devices that utilize biodegradable polymers have significant advantages over other competing delivery systems.[4,5] They improve the efficacy of drugs and eliminate the need for frequent administration.[5] Biodegradable polymeric microspheres are used to entrap small molecules, large proteins, and even DNA.[6] Microspheres are used as a type of delivery system for systemic administration of drugs, since they can be used to encapsulate and protect a wide variety of drug molecules, and their small size enable them to be injected.[6] Furthermore, if the polymer degrades only at the surface, the drug release process is simplified in that the water diffusion into the bulk is minimized and drug release rate is governed by polymer degradation rate. However, in practice this is not always the case. It has become evident that a more thorough understanding of the release mechanisms of sustained release formulations is necessary for precise design of controlled drug delivery systems, based on these polymers.[4]

Polyanhydrides are one of the few synthetic polymers employed in human patients for biomedical and drug delivery applications.[7,8] They have demonstrated good tissue biocompatibility *in vivo* and their breakdown products have shown no adverse toxicological effects.[9] Polyanhydrides are made of the most reactive functional group available for degradation on the basis of passive hydrolysis.[9] Polyadipic anhydride (PAA) is a fast degrading and surface-eroding aliphatic polyanhydre and it is biocompatible and degradable by simple hydrolysis, promoted *in vivo* by enzymatic activity.[10] Linear aliphatic polycarbonates have been investigated for use as medical implants[11] and for drug delivery applications.[12] Polytrimethylene carbonate (PTMC) has been shown to be suitable for these applications, being biocompatible and degradable by simple hydrolysis.[12] PTMC displays high elasticity at room temperature but degrades slowly in

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aqueous solution, showing little molecular weight loss, sample weight loss, or change in morphology after several months.[12] The high molecular weight polymer has a T_g close to room temperature.[13] It is thus in its rubbery state at room temperature. This allows for easy processing and for encapsulation of sensitive drugs under mild conditions.[12] Biodegradable blends of PTMC and PAA have been proven to be strong candidates for controlled drug delivery.[14] PAA functions as a plasticizer, permitting an increase in the erosion rate with the increase in the porosity and hydration.[12]

New effective analgesics are needed for treatment of pain. Buprenorphine a partial μ-opioid agonist, which has been in clinical use for over 25 years, has been found to be amenable to new formulation technology based on its physicochemical and pharmalogical profile. Buprenorphine is marketed as parentral, sublingual, and transdermal formulations.[15] Additionally, long acting buprenorphine delivery systems with cholesterol and glyceryltristearate[16] and biodegradable drug delivery system with PLGA[17] have been studied. Buprenorphine has been used for the treatment of acute and chronic pain, as a supplement of anesthesia, and for behavioral and psychiatric disorders, including treatment for opioid application. Prolonged use of buprenorphine can result in physical dependence.[15]

In this study, biodegradable microspheres intended for subcutaneous administration using polymeric blends of PTMC and PAA containing buprenorphine HCl were prepared and their drug release profile was studied. In the present work, PAA was synthesized via ring opening polymerization (ROP) of oxepan-2,7-dione and PTMC was synthesized from trimethylene carbonate (1,3 dioxan-2-one) via melt-condensation. These polymers were then blended together with different ratios, and used for the preparation of buprenorphine HCl microspheres. Since the use of water is prohibited because of stability problems of the PAA, microspheres were prepared by a nonaqueous oil-in-oil emulsion solvent removal method.[18]

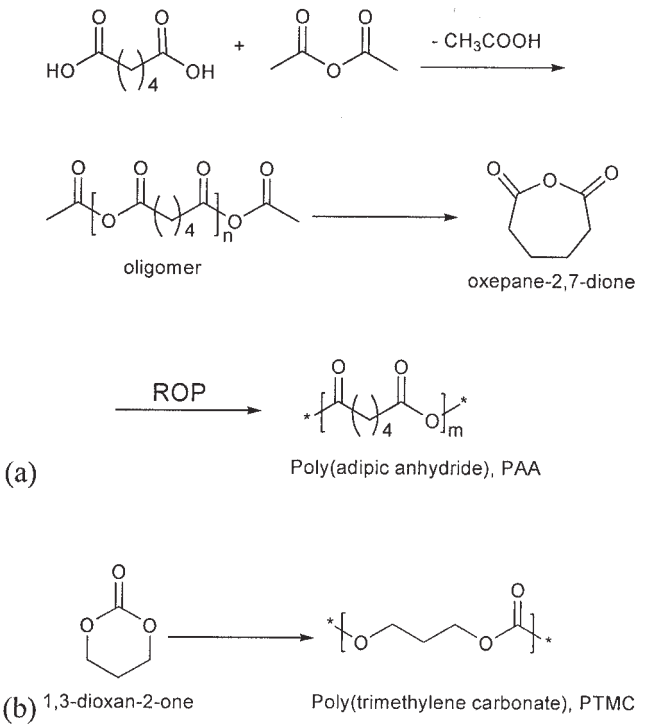

Figure 1 Schematic drawing of the synthesis of PAA from adipic acid (a), and PTMC from 1,3-dioxan-2-one (b).

MATERIALS AND METHODS

Materials

Adipic acid (extra pure) was purchased from Riedel-deHaen, Germany. Acetic anhydride, triethylamine, potassium phosphate monobasic, sodium hydroxide, toluene, diethyl ether, boron trifluride–ethyl ether complex and dichloromethane were purchased from Merck, Germany; petroleum ether was purchased from ParsChimie, Iran. Trimethylene carbonate (TMC) was purchased from Boheringer Ingelheim, Germany; methanol was purchased from Temad, Iran, Tween® 80 was purchased from, Seppic, France, and Arlacel® 83 was purchased from Uniqema, England. Buprenorphine HCl from Andard-Mount, UK, and silicone oil from Dow Corning, USA, kindly supplied by SOHA, Iran.

Polymer synthesis

Prepolymer was synthesized by boiling adipic acid in acetic anhydride for 5 h, while excesses acetic anhydride was distilled in low temperature under vacuum. Toluene was then added to the product and refluxed for 2 h. After the reaction had taken place, solvent was removed under vacuum and the product was dissolved in warm toluene and recrystallized.[19] The precipitates were washed with diethyl ether/petroleum ether (1:1 (v/v) mixture).[20] The solid product (prepolymer) was polymerized in bulk at 25°C for 1 h by using triethylamine (0.4 mol %) as a catalyst (Fig. 1a). The polymer was then recovered by dissolving the solid reaction product in dichloromethane and precipitating the solution in cold petroleum ether. After filtration, the polymer was dried to constant weight *in vacuo* (9 mbar).[20] The yield was approximately 70%.

PTMC was prepared by melt-condensation polymerization of 1,3-dioxan-2-one (TMC) in the bulk by using boron trifluoride etherate ($BF_3{\cdot}Et_2O$) (0.4 mol %), as a catalyst (Fig. 1b). The reaction temperature was 80°C, and the reaction time was 2 h. After polymerization, the polymer was dissolved in dichloromethane. The polymer was precipitated in methanol, fil-

TABLE I
Microspheres Formulations Prepared with Different Polymer Ratios

Formulation	PTMC (%)	PAA (%)	Buprenorphine HCl (%)
F1	55	45	5
F2	70	30	5
F3	85	15	5

tered, and dried *in vacuo* (9 mbar) at room temperature to constant weight.[22] The yield was approximately 90%. ^{1}H NMR spectra of polymer were shown to be similar to previously reported works.[12] ^{1}H NMR ($CDCl_3$): δ = 1.73 ppm (m, —CH_2—, 4H), δ = 2.53 ppm (m, —(CO) CH_2—, 4H), for PAA and δ = 2.05 ppm (quint., —CH_2—, 2H) , δ = 4.22 ppm (t, —OCH_2—, 4H) for PTMC.

Polymer characterization

The polymers were characterized for their melting point, molecular structure, and molecular weight using melting point apparatus, ^{1}H NMR and GPC, respectively. The melting points of prepolymers and polymers were determined using a melting point apparatus (MPD350.BM3.5, Gallenkamp, UK) with digital thermometer. The ^{1}H NMR spectra were obtained using a nuclear magnetic resonance spectrometer (Varian, 400, USA). The unity plus and chemical shifts (δ) were determined in ppm relative to the internal tetramethylsilane. The molecular weights of the polymers were estimated using a gel permeation chromatography (Shimadzu, 6A GPC system; Japan), using a copolymer column composed of styrene and divinyl benzene with 1000 Å pores and chloroform as the eluent, with a flow rate of 1.0 mL/min, at 40°C with a refractive index detector (Shimadzu, RID-6A; Japan). Polystyrene standards with narrow molecular weight distributions were used to calibrate the system.

Microspheres preparation

Microspheres with different ratios of polymer blends (Table I) and buprenorphine HCl were prepared by oil-in-oil emulsion solvent removal microencapsulation process.[10,16,17,21] Briefly, 4 g of polymer blend was dissolved in 50 mL dichloromethane. Then appropriate amount of buprenorphine HCl was dissolved/dispersed in the polymeric solution. The mixture was then homogenized and added drop wise into 200 mL silicone oil containing Arlacel 83 (0.5% (w/v)), and stirred at 300 rpm using overhead stirrer (RW20 IKA, Germany) with a three-blade impeller. After 3 h, 200 mL petroleum ether was introduced and the mixture was stirred for further 2 h. The microspheres were then isolated by filtration, washed three times with petroleum ether, and dried overnight under vacuum.

Microspheres drug content determination

The experimental amount of buprenorphine HCl loaded in the microspheres was determined by dissolving a weighed sample of microspheres in dichloromethane. The buprenorphine HCl content was then assayed spectrophotometrically at 288.8 nm. The theoretical drug loading in the microspheres was calculated by dividing the initial weight of buprenorphine HCl used by the initial weight of polymer and buprenorphine HCl used for the microspheres. Standard curves for determination of buprenorphine HCl was prepared using buprenorphine HCl, from 0 to 50 mg/L in dichloromethane.

Microspheres characterization

Particle size distributions were determined by laser light diffraction using a particle size analyzer (Mastersizer X, Malvern Instruments, UK). Microspheres were suspended in aqueous solution of 0.1% (w/v) Tween® 80 and desegregated for 2 min in an ultrasonic bath (US5/7, Fungilib, Spain). Scanning electron micrographs (SEM) were used to evaluate the morphology of microspheres. Samples were fixed on metal tubes and sputter-coated with gold and examined using digital scanning microscope (DSM960A, Zeiss, Germany). A differential scanning calorimeter (DSC-60, Shimadzu, Japan) was used for investigating the melting point and thermal properties of microspheres. The DSC was calibrated for temperature and enthalpy using the melting point of indium. Samples (5 mg) were contained in an aluminum pan, and an empty pan was used as a reference. Samples were heated from 20 to 200°C at 10°C/min. The DSC thermograms were analyzed to determine the melting point (T_m) and the enthalpy of melting (ΔH_m) of samples.

In vitro release of buprenorphine HCl

In vitro release studies of buprenorphine HCl from the microspheres were carried out to investigate the effects of different ratios of PTMC and PAA. 500 mg microspheres were dispersed in 10 mL (0.1*M*, pH 7.4) phosphate buffered aqueous medium in small glass containers and incubated in a shaking water bath (SBS30, Bibby Sterilin, UK), at 37°C. At different time intervals, the dispersion was centrifuged and samples were periodically collected and replaced by fresh buffer. Prior to sampling, the containers were centrifuged at 1000 rpm for 20 min to prevent microsphere contamination of the samples. The buffer was analyzed spectrophotometrically for buprenorphine HCl content at 285 nm using a spectrophotometer (UV-

TABLE II
Characteristics of Synthesized Polymers

Polymer	M_n (g/mol)[a]	M_w (g/mol)[a]	M_z (g/mol)[a]	M_w/M_n	M_z/M_n	Appearance
PAA	1354	1762	2223	1.30	1.64	White, brittle
PTMC	24,884	40,478	60,554	1.63	2.43	Clear, soft, rubbery

[a]Measured by GPC in $CHCl_3$ at 40°C.

1601, Shimadzu, Japan). The cumulative release of buprenorphine HCl was calculated. The monitoring of drug release was continued for 50 days. Standard curves for determination of buprenorphine HCl was prepared using buprenorphine HCl, from 0 to 50 mg/L in phosphate buffer (pH 7.4).

Release kinetics

The release profiles were evaluated independently for the type of release kinetics observed; zero order, squared root of time and first order. Zero order release rate constant (k_0) were estimated from the initial linear portion of the profiles. The release profiles were thus fitted to the following equation using a nonlinear regression software, SPSS 12.0, to obtain the first order release rate constant, k_r (day^{-1}), and A_0 (mg), the total amount of drug that will be eventually released:

Cumulative amount of drug released (mg) = A_0 (mg) $(1-e^{k_r t})$.[22]

RESULTS AND DISCUSSIONS

The melting point of PAA prepared in this study was 73–75°C, which is similar to previously reported works.[12,20]. The molecular weights (M_n and M_w) and molecular weight distribution (M_z/M_n, M_w/M_n) and the appearance of the synthesized polymers are shown in Table II.

Polyanhydrides are quickly degraded in aqueous solutions[10,20] It is therefore preferred to prepare PAA microspheres in organic solvents. Microsphere preparation by solvent removal method is, in principal, quite simple and involves two major steps: (a) the formation of stable droplets of the polymer–drug solution and (b) the subsequent removal of solvent from the droplets[10],[18] and[23]. In this study, dichloromethane was used as the volatile organic phase as it is a good solvent for the PAA and PTMC. The drug, buprenorphine HCl, is however less soluble in dichloromethane. To achieve higher drug loadings, buprenorphine HCl was used at concentrations above the saturation point of buprenorphine HCl in dichloromethane. The polymer/drug mixture was then emulsified in an oil phase, silicone oil, containing Arlacel 83 (0.5% (w/v)). Microspheres were formed after extraction of dichloromethane by the continuous phase. The use of oil-in-oil extraction technique is most appropriate for the microspheres preparation in this study, as the tendency for the hydrophilic drug to diffuse out from the dichloromethane–polymer droplets to the surrounding silicone oil phase is very low. The theoretical and actual drug loadings are summarized in Table III.

The actual amount of buprenorphine HCl loaded in the microspheres was determined by dissolving 500 mg of microspheres in dichloromethane. The buprenorphine HCl content was then assayed spectrophotometrically at 288.8 nm. Microsphere yield was calculated by eq. 1.

$$\textit{Microsphere yield}\ (\%) = (\textit{microspheres obtained}\ (mg)/\textit{polymer}\ (mg) + \textit{buprenorphine HCl}\ (mg)) \times 100 \quad (1)$$

Drug loading efficiency was also calculated by eq. 2.

$$\textit{Drug loading efficiency}\ (\%) = (\textit{actual buprenorphine HCl content}\ (mg)/\text{theoretical buprenorphine HCl content (mg)}) \times 100 \quad (2)$$

Three different loadings (2, 5, and 10% (w/w)) were studied. For drug loadings of 2 and 5%, the Drug

TABLE III
Microspheres Yield (%) and Drug Loading Efficiency of PTMC–PAA Microspheres

Formulation	Polymer content (mg)	Buprenorphine HCl (mg)	Microspheres obtained (mg)	Microspheres yield (%)	Drug loading efficiency
Sample 1	500	50	520	89.65	70.16
Sample 2	500	25	518	98.66	95.20
Sample 3	500	10	502	98.43	97.20

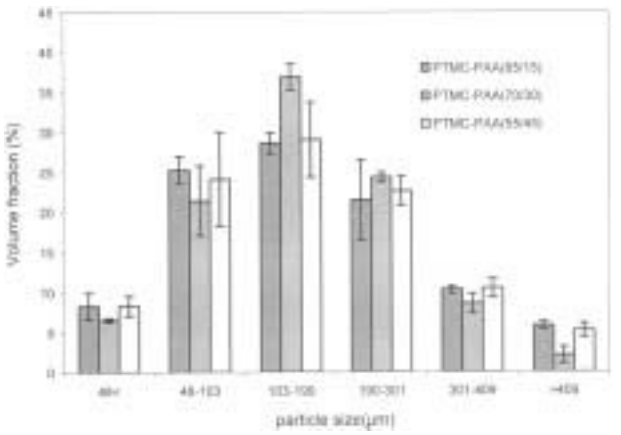

Figure 2 Size distribution of PTMC–PAA microspheres containing of 5% buprenorphine HCl: (a) PTMC–PAA (85/15), (b) PTMC–PAA (70/30) and (c) PTMC–PAA (55/45) (experiment was repeated 3 times, mean ± SD).

loading efficiency was 97 and 95%, respectively. For drug loading of 10%, the Drug loading efficiency was only 70%. This lower drug loading efficiency may be due to the limited solubility of buprenorphine HCl in dichloromethane.

The microspheres had a relatively broad size distribution (Fig. 2). However, 80% of the microspheres had a size range of 60–414 μm, with an average size of 209 μm for PTMC–PAA (85/15), 70–357 μm, with an average size of 197 μm for PTMC–PAA (70/30), and 61–407 μm, with an average size of 209 μm for PTMC–PAA (55/45) microspheres (Table IV). Scanning electron micrographs (SEM) of 5% loaded PTMC–PAA microspheres are shown in Figure 3. The observation by SEM showed that the drug loaded microspheres were spherical in shape and displayed an external surface covered with small particles of buprenorphine HCl crystals. The surface of microspheres with higher amount of PTMC (Fig. 3c) was smoother than those with less amount of PTMC (Figs. 3a and 3b).

Experiments for characterization of buprenorphine HCl-loaded microspheres by DSC were carried out to determine the melting point (T_m) and enthalpy of melting (ΔH_m) of the polymeric blend microspheres with 5% drug loading (Table V). As shown in Table V, with increase in the PTMC ratio of microspheres, melting point and enthalpy of melting of the polymeric

TABLE IV
Particle Size Distribution of PTMC–PAA Microspheres Containing of 5% Buprenorphine HCl

Formulation	$D_{10\%}$ (μm)	$D_{50\%}$ (μm)	$D_{90\%}$ (μm)
PTMC–PAA (85/15)	60.69 ± 0.91	172.59 ± 4.32	414.14 ± 3.31
PTMC–PAA (70/30)	70.30 ± 1.05	177.14 ± 4.43	357.83 ± 2.86
PTMC–PAA (55/45)	60.91 ± 0.94	176.52 ± 4.41	407.07 ± 3.26

Experiment was repeated 3 times; values given are mean ± SD.

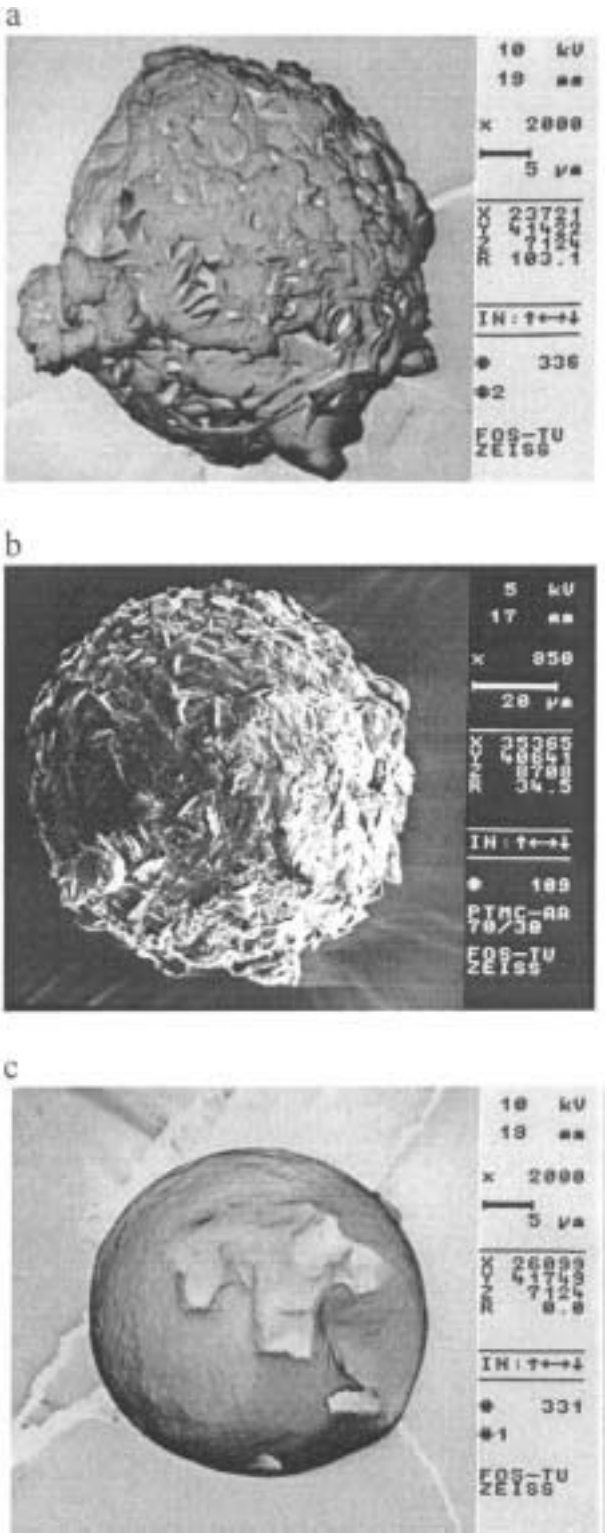

Figure 3 Scanning electron micrograph of (a) PTMC–PAA (55/45), (b) PTMC–PAA (70/30), and (c) PTMC–PAA (85/15) blend microspheres containing 5% buprenorphine HCl.

TABLE V
Correlation Between Melting Point and Enthalpy of Melting of Drug Loaded Microspheres with Different Ratios of PTMC–PAA

Formulation	T_m (°C)	ΔH_m (J/g)
PAA	64.6	−53.17
PTMC–PAA (55/45)	61.8	−46.59
PTMC–PAA (70/30)	56.6	−19.70
PTMC–PAA (85/15)	53.5	−12.83

blend decreased. DSC results showed that the T_g of PTMC and T_m of PAA in the blend are lower than those in the homopolymers. This decrease in T_m may be attributed to the plasticization effect of the blending[24].

The release profiles of 500 mg PTMC–PAA (55/45), PTMC–PAA (70/30), and PTMC–PAA (85/15) microspheres containing 5% buprenorphine HCl are shown in Figure 4. Drug release from PTMC–PAA (55/45) microspheres was faster than PTMC–PAA (70/30) microspheres and much faster than PTMC–PAA (85/15) microspheres. At first 3 days of drug release experiment PTMC–PAA (55/45), PTMC–PAA (70/30), and PTMC–PAA (85/15) microspheres released 56, 27, and 15% of their drug content, respectively. This shows that the more is the percentage of PAA content of the polymeric blend, the faster is the drug release from PTMC–PAA microspheres. This is obviously due to the faster biodegradability rate of PAA in comparison to PTMC. Additionally, the *in vitro* release profiles were compared by using a one-way analysis of variance (ANOVA). The difference between the three sets of drug release was significant ($P < 0.01$)

The release profiles were also evaluated independently for the type of release kinetics observed; zero order, square root of time and first order. R^2 results for

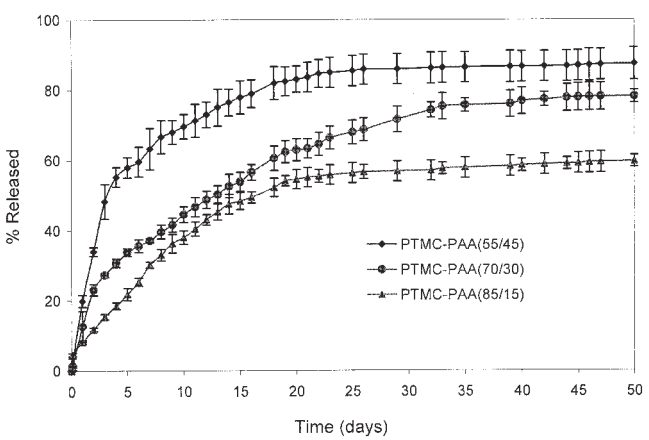

Figure 4 Effect of PTMC/PAA ratio on buprenorphine HCl release from PTMC–PAA blend microspheres containing of 5% buprenorphine HCl in phosphate buffer (pH = 7.4) at 37°C ($n = 3$, mean ± SD).

TABLE VI
R^2 Values for the Different Release Kinetics Model from Microspheres with Different Ratios of PTMC/PAA Containing 5% Buprenorphine HCl ($n = 3$)

Formulation	Linear equation and R^2 value	K_0 (mg/day)[a]
PTMC–PAA (55/45)	$Y = 18.2050x + 0.3670$ ($R^2 = 0.9925$)	6.3400 ± 0.0013
PTMC–PAA (70/30)	$Y = 9.1739x + 2.4588$ ($R^2 = 0.9403$)	3.1950 ± 0.0106
PTMC–PAA (85/15)	$Y = 3.4652x + 4.5478$ ($R^2 = 0.9954$)	1.2068 ± 0.0008

first three days, 4th day and up to 50 days and total release profile (from days 0–50) are summarized in Table VI. Although there was no single kinetic model that could explain the entire release profile of buprenorphine HCl from PTMC–PAA microspheres with different ratios of PTMC/PAA content, it appeared that the release of buprenorphine HCl from microspheres in first three days followed approximately zero order release kinetics. Zero order release constants (k_0) calculated from the initial linear portion of the release profiles (after 2 h, one, two, and three days) are listed in Table VII. The rate of drug release from microspheres appeared to increase with increase in the PAA ratio. It may be reasonable to assume that in first three days the amount of PAA determines the release rate of buprenorphine HCl from microspheres. The regression equations and first order release rates constant (k_r) are summarized in Table VIII. As can be seen, the kinetics of drug release from microspheres after the first three days follows first order release kinetics. The release rate constants (k_r) were different for each kind of microspheres. It appears that diffusion is the main mechanism of drug release after the first three days.

CONCLUSIONS

It can be concluded that the rate of drug release from microspheres prepared using PTMC–PAA blends can be successfully controlled. It was shown that the rate of drug release from microspheres is a function of the

TABLE VII
Zero Order Release Rate Constants (k_0) for Drug Release from Microspheres with Different Ratios of PTMC/PAA Containing 5% Buprenorphine HCl ($n = 3$)

Formulation	R^2 value	K_r (1/day)[a]
PTMC–PAA (55/45)	0.9747	0.5836 ± 0.0512
PTMC–PAA (70/30)	0.9696	0.8056 ± 0.0731
PTMC–PAA (85/15)	0.9927	0.7765 ± 0.0367

[a]Zero order release rate (mg/day) obtained using linear regression of the initial linear part of the release profile.

TABLE VIII
First Order Release Rate Constant (k_r), for Drug Release from Different Ratios of PTMC and PAA Blend Microspheres (n = 3)

Formulation	R^2 value	K_r (1/day)[a]
PTMC–PAA (55/45)	0.9747	0.5836 ± 0.0512
PTMC–PAA (70/30)	0.9696	0.8056 ± 0.0731
PTMC–PAA (85/15)	0.9927	0.7765 ± 0.0367

[a]First order release rate constant (day^{-1}) obtained using the following equation: $A(t)$ (mg) = A_0 (mg) × (1 − $e^{kr\ t}$), t = time (days).

PTMC–PAA ratio. The combination of faster biodegradation of PAA and slower biodegradation of PTMC could provide for the initial burst release of buprenorphine HCl and its continued slower release for the rest of the drug delivery period.

References

1. Dinarvand, R.; Alimorad, M. M.; Amanlou, M.; Akbari, H. J Biomed Mater Res A 2005, 75, 185.
2. Dinarvand, R.; Moghadam, S. H.; Mohammadyari-Fard, L.; Atyabi, F. AAPS Pharm Sci Tech 2003, 4, article 34.
3. Jiang, J.; Kojima, N.; Guo, L.; Naruse, K.; Makuuchi, M.; Miyajima, A.; Yan, W.; Sakai, Y. Tissue Eng 2004, 10, 1577.
4. Shen, E.; Kipper, M. J.; Dziadul, B.; Lim, M.-K.; Narasimhan, B. J Controlled Release 2002, 82, 115.
5. Woo, B. H.; Kostanski, J. W.; Gebrekidan, S.; Dani, B. A.; Thanoo, B. C.; DeLuca, P. P. J Controlled Release 2001, 75, 307.
6. Sandor, M.; Bailey, N. A.; Mathiowitz, E. Polymer 2002, 43, 279.
7. Akbari, H.; D'Emanuele, A.; Attwood, D. Int J Pharm 1998, 160, 83.
8. Chan, C.-K.; Chu, I.-M. Biomaterials 2002, 23, 2353.
9. Davies, M. C.; Khan, M. A.; Domb, A.; Langer, R.; Watts, J. F.; Paul, A. J. J Appl Polym Sci 1991, 42, 1597.
10. Albertsson, A.-C.; Carlfors, J.; Sturesson, C. J Appl Polym Sci 1996, 62, 695.
11. Pego, A. P.; Van Luyn, M. J.; Brouwer, L.A.; van Wachem, P. B.; Poot, A. A.; Grijpma, D. W.; Feijen, J. J Biomed Mater Res 2003, 67, 1044.
12. Edlund, U.; Albertsson, A. C. J App Polym Sci 1999, 72, 227.
13. Smith, M. J.; Silva, M. M.; Cerqueira, S.; MacCallum, J. R. Solid State Ionics 2001, 140, 345.
14. Edlund, U.; Albertsson, A. C.; Singh, S. K.; Fogelberg, I.; Lundgern, B. O. Biomaterials 2000, 21, 945.
15. Johnson, R. E.; Fudala, P. J.; Payne, R. J Pain Symptom Manage 2005, 29, 297.
16. Pontani, R. B.; Misra, A. L. Pharmacol Biochem Behav 1983, 18, 471.
17. Mandal, T. K. Drug Dev Ind Pharm 1999, 25, 773.
18. Mathiowitz, E.; Saltzman, W. M.; Domb, A.; Dor, P. H.; Langer, R. J Appl Polym Sci 1988, 35, 755.
19. Domb, A. J.; Gallardo, F. C.; Langer, R. J. Polym Sci Part A: Polym Chem 1987, 25, 3373.
20. Albertsson, A.-C.; Eklund, M. J. Appl Polym Sci 1995, 57, 87.
21. Hill, J. W. J Am Chem Soc 1930, 52, 4110.
22. Park, E.-S.; Maniar, M.; Shah, J. C. J Controlled Release 1998, 52, 179.
23. Herrmann, J.; Bodmeier, R. Eur J Pharm Biopharm 1998, 45, 75.
24. Albertsson, A.-C.; Liu, Y. J Macromol Sci Pure Appl Chem 1997, 34, 1457.