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RESEARCH PAPER

Sustained-Release Butorphanol Microparticles

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ABSTRACT

Various butorphanol-loaded microparticles have been prepared with a biodegradable copolymer P(FAD-SA) of erucic acid dimer (FAD) and sebacic acid (SA) and a copolymer P(CPP-SA) of carboxyphenoxypropane (CPP) and SA using a melt compounding and milling method. Drug release was measured in vitro following incubation of drug-loaded microparticles in water for injection at 37°C. It was found that butorphanol was released in a sustained manner, yielding a cumulative drug release of about 100% over a period of 48 hr. Also, drug release was affected by drug loading and the size of the microparticles; however, it was not significantly influenced by the copolymer composition. Scanning electron microscopic (SEM) results showed that most of the particles were irregular in shape with uneven surfaces. The molecular weights of the copolymers were not changed after this fabrication process. In addition, 20% butorphanol-encapsulated microspheres were prepared with copolymer P(FAD-SA) by spray-drying. The SEM micrograph shows that the particle sizes of the microspheres ranged from 2 to 10 μm, and the external surfaces appear smooth. Moreover, rapid drug release was observed for these microspheres, with more than 92% of the encapsulated drug released within the first 2 hr.

Key Words: *Butorphanol; CPP-SA; FAD-SA; Microparticles; Microspheres; Polyanhydride; Sustained release.*

INTRODUCTION

Butorphanol, a synthetic morphinan derivative, was developed to minimize side effects associated with classical narcotic analgesics such as morphine and codeine (1). It has been classified as a potent opioid analgesic with both agonist and antagonist effects. The analgesic potency of butorphanol is 3.5 to 7 times that of morphine, 30 to 40 times that of meperidine, 15 to 20 times that of pentazocine, and 1/40 that of naloxone (2). Butorphanol also has a strong antitussive effect that is 100 times that of codeine (3).

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Butorphanol is commonly used for the relief of moderate to severe pain and as an adjunct to anesthesia. However, butorphanol is absorbed and excreted rapidly in the body, and its duration is relatively short. This is because butorphanol has a short half-life ($t_{1/2}$ about 1.5–3 hr). It was reported that the onset of analgesia is within 10 min of intramuscular injection and may last for 3 to 4 hr. For the relief of moderate-to-severe pain, the usual dose is 1–4 mg of the tartrate salt given intramuscularly or 0.5–2 mg given intravenously every 3 to 4 hr in humans (3). To provide a therapeutic duration longer than 1 day, the use of a parenteral controlled-release preparation is a very attractive alternative. The incorporation of a drug into a controlled-release system can provide sustained release of the drug and slower uptake of the drug into the systemic circulation. Thus, the duration of drug action can be prolonged and the therapeutic index can also be improved by reducing its systemic toxicity.

The use of biodegradable polymers as drug delivery systems for controlled release of medications has grown tremendously in recent years. A major advantage of using a biodegradable drug delivery system over others is that it does not require the surgical removal of the drug-depleted device. Several types of biodegradable polymers, including poly(aliphatic esters), poly(orthoesters), poly (phosphate esters), and polylactic acid polymers, have been employed as biodegradable polymers for drug delivery, and their advantages and disadvantages have been reviewed elsewhere (4,5). The current investigation describes the potential application of polyanhydride microspheres and microparticles for parenteral sustained release of butorphanol.

In this study, spray-drying, a fast and reproducible method, is used for preparing microspheres. In addition, a simple and solvent-free extrusion compounding method coupled with a milling process is employed to prepare drug-loaded microparticles. The objective of this study was to investigate whether the polyanhydride microspheres or microparticles can provide in vitro release of butorphanol for 48–72 hr and thus potentially prolong the pain relief effect of butorphanol over days.

The following polymers were evaluated: copolymers of erucic acid dimer (FAD) with sebacic acid (SA) at a weight ratio of 1:1 and copolymers of 1,3-bis(carboxyphenoxy-propane) (CPP) with SA at a weight ratio of 1:4. In general, polyanhydride copolymers are synthesized using a hydrophobic monomer (FAD or CPP) and a hydrophilic monomer such as SA. The release characteristics of the drug from the particulate polyanhydride polymeric delivery system were evaluated with respect to drug loading, particle size, and composition of the polymer matrix in terms of the hydrophobic and hydrophilic components.

EXPERIMENTAL

Materials

Butorphanol tartrate, P(FAD-SA) 1:1, and P(CPP-SA) 1:4 are products of Abbott Laboratories (North Chicago, IL). Methylene chloride was purchased from EM Science (Gibbstown, NJ). Tween 20 was obtained from Aldrich (Milwaukee, WI).

Methods

Preparation of Spray-Dried Butorphanol Tartrate

The butorphanol tartrate used in the preparation of drug-loaded polyanhydride microspheres or microparticles was a spray-dried product. For preparation, 16 g of bulk butorphanol tartrate were dissolved in 500 ml of water for injection, and this aqueous solution was then spray-dried using the Büchi Mini Dryer, model 191 (Flawil, Switzerland), under the following conditions: compressed N_2 at 70 psi; inlet temperature 130°C; outlet temperature 74°C; spray flow at 600 L/hr; aspirator setting at 100%; pump flow at about 9 ml/min with an 0.5-mm nozzle.

Preparation of Microspheres by Spray-Drying

Microspheres were prepared using a spray-dried method with the Büchi Mini Dryer. Copolymer P(FAD-SA) 1:1, 1.6 g, was dissolved in 50 ml of methylene chloride, followed by dispersing 0.4 g spray-dried butorphanol tartrate in this polymer solution using a mechanical mixer. The dispersion was then sonicated in a bath-type sonicator for 5 min prior to spray-drying. The dispersion was spray-dried under the following conditions: compressed N_2 at 68 psi; inlet temperature 41°C; outlet temperature 33°C; spray flow at 600 L/hr; aspirator setting at 100%; pump flow at about 9 ml/min with an 0.5-mm nozzle.

Preparation of Microparticles by Compounding and Milling

The spray-dried butorphanol tartrate was blended with a predetermined weight of P(FAD-SA) 1:1 or P(CPP-SA) 1:4 copolymer powder with 20% or 30% drug loading in a glass jar. The preblended drug-copolymer powder mixtures were loaded into a DACA® twin-screw compounder (Goleta, CA) and kneaded in the barrel at

75°C (~5°C above the melting temperature of the copolymer) at a 100 rpm mixing speed for 3 min. The molten mixture was subsequently extruded through an orifice with a 1.0-mm opening and collected as strands. These strands were milled using a Bel-Art® Micro-Mill (Pequannock, NJ) and sieved through a series of U.S. standard testing sieves with aperture sizes of 425, 300, and 212 μm. Microparticles in the following size ranges were collected for further evaluation: 300–425 μm, 212–300 μm, and <212 μm.

Scanning Electron Microscopy

Surface morphologies of the microspheres and microparticles were characterized by scanning electron microscopy (SEM). The samples were mounted on metal stubs and sputter coated with gold using a Denton® model Desk-II sputter (Cherry Hill, NJ). A Stereoscan S-260 electron microscope (LEO Electron Microscopy, Inc., Cambridge, England) was used.

Molecular Weight

Molecular weight determinations were made using a Waters GPC (gel permeation chromatography) system with Waters® Styragel HR-5E linear column (Marlborough, MA). Methylene chloride was used as the eluent. Detection was accomplished using a refractive index detector (RID). Conditions of operation were as follows: injection volume was 10 μl, flow rate was 1 ml/min, and solute concentration was 19 mg/ml. Monodispersed polystyrene standards were used to calibrate the GPC system. This allowed the computation of the unknown sample molecular weights by correlating the retention time or volume with a molecular weight distribution curve. The weight-average molecular weights were calculated using the following equation:

$$M_w = \frac{\sum hiMi}{\sum hi}$$

where *hi* is the baseline-corrected height of data point *i*, and *Mi* is the molecular weight of data point *i* as obtained from the calibration curve. An average of four determinations was made for each sample.

Differential Scanning Calorimetry

The thermal properties, melting point T_m, and heat of fusion ΔH, of the copolymers in microparticles were determined on a Perkin-Elmer DSC-2 differential scanning calorimeter (DSC; Norwalk, CT). Predetermined amounts of samples were weighed and crimped into aluminum pans. Samples were heated from 230 K to 425 K at 10°C/min and then quenched to 230 K. They were then reheated under the same conditions. The system was calibrated using an indium standard.

Drug Content

To determine the drug content, drug-loaded microspheres or microparticles (25 mg) were dissolved in 2 ml of chloroform. The drug was extracted by 10 ml of 0.1 N H_2SO_4. After being mixed for 1 hr and being centrifuged at 2500 rpm for 10 min, an aliquot (5 ml) was diluted to 100 ml with water for injection. The resulting solution was then directly injected onto a high-performance liquid chromatograph (HPLC).

The HPLC system consisted of a Shimadzu® (Columbia, MD) model SIL-9A autoinjector, a Shimadzu model SPD-6A UV spectrophotometer, a Shimadzu model LC-6A liquid chromatograph, and a Shimadzu model CR501 integrator. The stationary phase was a μBondapak™ phenyl column (3.9 × 300 mm, Waters, USA). The mobile phase was prepared by mixing 1 L of 0.05 M ammonium acetate and 335 ml of acetonitrile, with pH adjusted to 4.1 using glacial acetic acid. The chromatogram was monitored by UV detection at the maximum wavelength of 280 nm with a sensitivity setting of 0.04 AUFS. The injection volume was 100 μl, and the flow rate was 2 ml/min. Each determination was made in triplicate.

In Vitro Drug Release

For in vitro drug release study, 25 mg of microspheres or microparticles were added in duplicate to 100 ml of water for injection (pH 5.80) containing 0.02% (w/w) Tween 20. The mixture was slowly agitated by hand for 2 min to resuspend the materials. Agitation was achieved using a reciprocal shaker bath (Precision® model 50, Winchester, VA) at 37°C and 120 rpm. At predetermined sampling time intervals, 1 ml of the dissolution medium was withdrawn and replaced by 1 ml of fresh water for injection. The drug concentration of the aliquot was measured using the HPLC method described in the previous section. The drug release study was conducted under sink conditions. The drug release data reported in this study are an average of duplicate samples.

RESULTS AND DISCUSSION

Microsphere Preparation by Spray-Drying

In this study, only copolymer P(FAD-SA) 1:1 was spray-dried to encapsulate butorphanol tartrate. The polymer was first dissolved in methylene chloride, and the

insoluble butorphanol tartrate was suspended as particles in the polymer solution. When a suspension is spray-dried, it is very important to use small drug particles since the nozzle of the spray dryer is only 0.5 mm. In our study, butorphanol tartrate particles (1–5 μm) were obtained by spray-drying an aqueous butorphanol tartrate solution. These spray-dried drug particles were subsequently suspended in the polymer solution (methylene chloride) and processed as described above. The yield of the microspheres was about 66% by weight. The viscosity of the polymer solution has a great impact on the yield. A polymer solution with a higher viscosity tends to cause more aggregation, yielding more undried polymer sticking to the drying chamber and resulting in a lower yield. It was found that 4–10% (w/v) of FAD-SA (1:1) copolymer in methylene chloride could result in a desirable yield.

Preparation of Microparticles by Compounding and Milling

In this study, butorphanol-loaded copolymer microparticles were prepared using a DACA® twin-screw compounder (Goleta, CA), which can be used to process a small scale (<5 g) of material within a very short time (20 min) with precise control of mixing time, temperature, and speed. The most important feature of this technique is that the entire process does not involve any organic solvent, an important advantage in an industrial process.

Shape and Size of Microspheres and Microparticles

An SEM of butorphanol-loaded microspheres prepared with P(FAD-SA) 1:1 by spray-drying is presented in Fig. 1a. These microspheres are spherical in shape with smooth external surfaces. It is revealed that a mild degree of aggregation occurs between particles. Most of the particles are in the size range 2–10 μm.

A representative SEM of microparticles (212–300 μm) loaded with 20% butorphanol prepared with P(FAD-SA) 1:1 by compounding and milling is presented in Fig. 1b. Most of the particles are irregular in shape with uneven surfaces (Fig. 1c).

Molecular Weight

The molecular weights of copolymer P(FAD-SA) 1:1 and P(CPP-SA) 1:4 before and after melt compounding

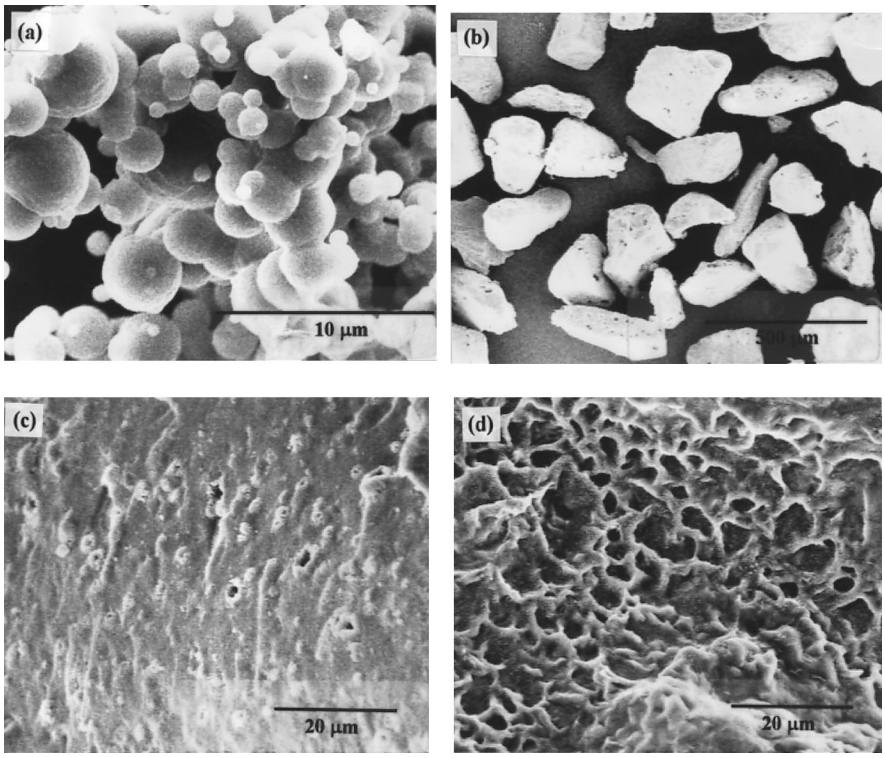

Figure 1. SEM of (a) 20% drug-loaded P(FAD-SA) 1:1 microspheres; (b) 20% drug-loaded P(FAD-SA) 1:1 microparticles 212–300 μm in size at lower magnification; (c) higher magnification of Fig. 1b; (d) microparticles of Fig. 1b after 48 hr dissolution.

Table 1

Molecular Weight Characteristics of the Copolymers Before and After Compounding and Milling

	MW_w Before Process	MW_w After Process: 20% Loading	MW_w After Process: 30% Loading
P(FAD-SA) 1:1	29,692	29,015	26,285
P(CPP-SA) 1:4	17,741	16,984	NA[a]

[a] NA = not available.

Table 2

Characterization of Microparticles by Differential Scanning Calorimetry

Polymer	% Loading	T_m (°C)	ΔH (J/g)
Pure P(FAD-SA) 1:1	—	70.9	68.6
P(FAD-SA) 1:1	20	67.1	55.9
P(FAD-SA) 1:1	30	66.6	46.9
Pure P(CPP-SA)1:4	—	71.1	65.5
P(CPP-SA) 1:4	20	58.5	45.5

and milling are given in Table 1. It is apparent that the molecular weight changes of P(FAD-SA) 1:1 or P(CPP-SA) 1:4 were insignificant after drug incorporation and melt compounding and milling.

Characterization of Microparticles by Differential Scanning Calorimetry

In the current study, the compounding and extrusion process requires the application of an elevated temperature that is about 5°C above the melting point of the copolymer. The melting of the copolymer during the compounding process is critical to the effective mixing of the drug particles in the copolymer matrix. The melting points of the copolymer before and after compounding and milling were monitored. The melting points and heats of fusion for pure P(FAD-SA) 1:1 and pure P(CPP-SA) 1:4 are shown in Table 2. When microparticles consisting of P(FAD-SA) 1:1 copolymer are examined, there is only a minimal decrease in their melting point, with 20% (67.1°C) or 30% (66.6°C) drug loading compared to the pure polymer (70.9°C). On the other hand, in the case of P(CPPA-SA) 1:4, a dramatic decrease in the melting point of drug-loaded copolymer (58.5°C) compared to the pure copolymer (71.1°C) was seen. The decrease in the melting point of the drug-polymer mixture may indicate a drug-polymer chemical interaction (6). Furthermore, there were pronounced decreases in the heat of fusion for both drug-loaded P(FAD-SA) and drug-loaded P(CPPA-SA) copolymer compared to the pure copolymer. The decrease in the heat of fusion may indicate a reduction in the crystallinity of the copolymers during fabrication (7).

Drug Content

Data in Table 3 show that encapsulation efficiency was high (92.5%) for butorphanol-loaded microspheres prepared by spray-drying. The actual drug contents for the microparticles were all close to 100% of the theoretical loadings. These results indicate that both fabrication processes are capable of preparing drug-loaded polyanhydride microspheres and microparticles with high content uniformity.

In Vitro Drug Release

The in vitro drug release was relatively fast for 20% butorphanol-loaded P(FAD-SA) 1:1 microspheres pre-

Table 3

Drug Content of Butorphanol in Microspheres and Microparticles

Polymer	Size	Expected (%)	Experimental[a] (%)
Microspheres			
P(FAD-SA) 1:1	2–10 μm	20	18.5 ± 0.7
Microparticles			
P(FAD-SA) 1:1	300–425 μm	20	19.9 ± 0.4
P(FAD-SA) 1:1	212–300 μm	20	20.9 ± 0.6
P(FAD-SA) 1:1	<212 μm	20	20.8 ± 0.1
P(FAD-SA) 1:1	300–425 μm	30	29.3 ± 0.1
P(CPP-SA) 1:4	300–425 μm	20	20 ± 0.5

[a] $n = 3$.

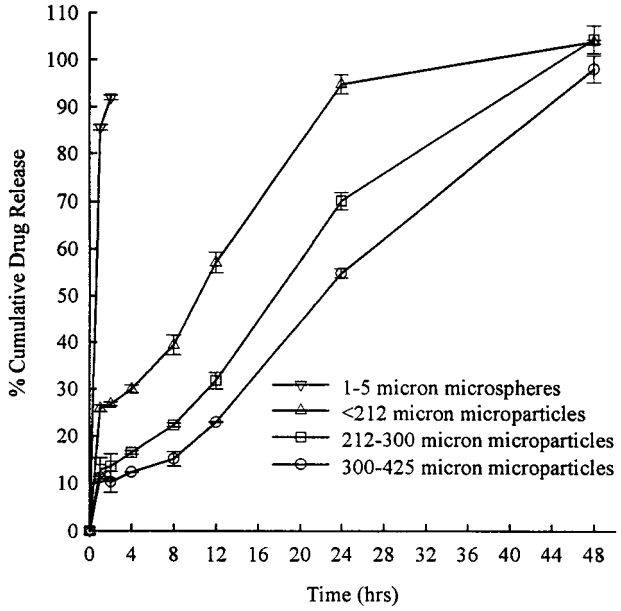

Figure 2. Effect of particle size on drug release of 20% butorphanol-loaded P(FAD-SA) 1:1 microparticles.

pared by spray-drying. As shown in Fig. 2, more than 92% of the encapsulated drug was released within 2 hr. This fast release may be attributed to the small size of the microspheres (2–10 μm) and the vast surface area. Also, it is very likely that only a single drug particle was embedded in each microsphere since the size of microspheres was approximately the same size as the drug particles (1–5 μm). Therefore, fast dissolution of the encapsulated drug could take place immediately when the drug particle was exposed to the aqueous environment. The results suggest that the small-size microspheres prepared in this study were not a sustained-release system for butorphanol.

Figure 2 also shows that the drug release profiles for the various sizes (<212 μm, 212–300 μm, and 300–425 μm) of 20% drug-loaded microparticles prepared with P(FAD-SA) 1:1. A small burst effect was exhibited in all drug release profiles at the first hour, and the extent of the burst effects increased with decreasing microparticle size. Since butorphanol tartrate is highly soluble in aqueous solution, the burst effect is probably caused by the immediate dissolution of the drugs located on the surface of the microparticles. The dissolution of the surface drug will result in channels, allowing the aqueous medium to penetrate into the matrix, leading to drug dissolution and subsequent drug release via the medium-filled channels. This is evidenced by the SEM micrograph in Fig. 1d, which shows the formation of pores on the external surface of the microparticles after drug dissolution for 48 hr. Figure 2 also shows that smaller size microparticles released butorphanol at a faster rate than those of a larger size. The cumulative percentages of drug release at 24 hr was 55%, 70%, and 94% for particles with sizes 300–425 μm, 212–300 μm, and <212 μm, respectively. However, total drug release approached 100% at 48 hr for microparticles of all three sizes.

In our earlier study, we characterized drug release in vitro following incubation of the drug-loaded P(FAD-SA) microparticles in phosphate buffer, pH 7.4, at 37°C, to mimic physiological conditions. However, only about 60% of the drug was released in the dissolution media after 72 hr, and no more drug could be recovered after that. It is speculated that butorphanol, with an active alcohol group, may interact with some of the hydrolyzed polymer during the process of polymer degradation and drug release in phosphate buffer solutions. This drug-polymer interaction during drug release in aqueous solutions has also been studied by other investigators (8). To minimize the drug-polymer interaction problems during drug release, it was determined that we would continue our in vitro drug release study in water for injection, pH 5.8.

In Fig. 3, drug release is compared for microparticles containing two different drug loadings (30% vs. 20%). It

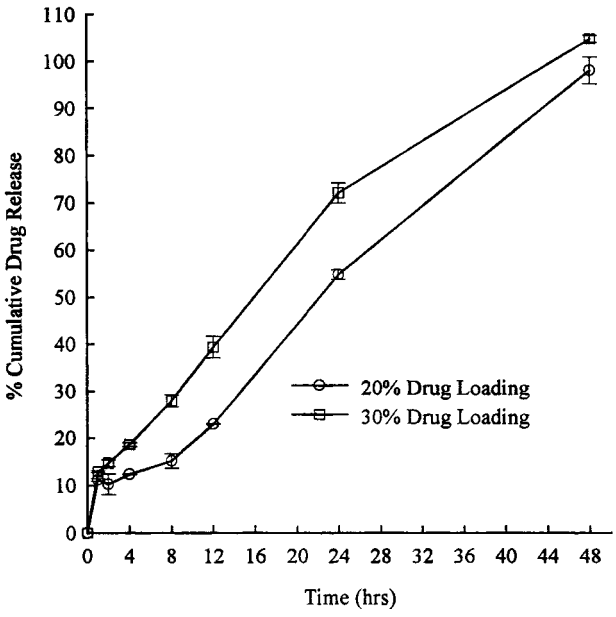

Figure 3. Effect of drug loading on drug release of butorphanol-loaded P(FA-SA) 1:1 microparticles 300–425 μm in size.

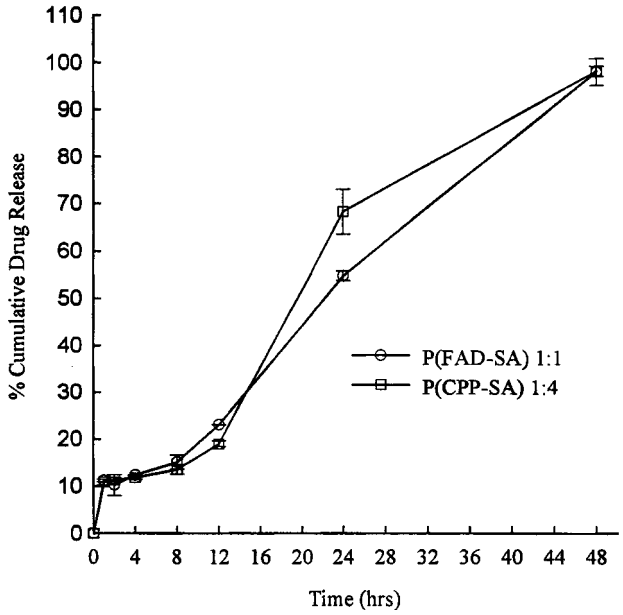

Figure 4. Effect of polymer composition on drug release of 20% butorphanol-loaded microparticles 300–425 μm size.

was found that the rate of drug release increased with a higher drug/copolymer ratio. This result may suggest that, at low drug loading (20%), each drug particle is embedded in a matrix with 80% of the hydrophobic copolymer, and drug release can be more effectively retarded by the copolymer (7). However, with higher drug loading (30%), the dissolution of the drug possibly produced more pores and channels for the diffusional transport of the drug, leading to a faster drug release.

P(FAD) is an aliphatic polymer, and P(CPP) is an aromatic polymer. Both P(FAD) and P(CPP) are relatively hydrophobic and are copolymerized with a more hydrophilic monomer, sebacic acid, used in this study. The effect of copolymer composition, P(FAD-SA) versus P(CPP-SA), on drug release is compared in Fig. 4. It was found that the drug release shown in Fig. 4 in the microparticles made with P(FAD-SA) was not significantly different in the first 16 hr from that in the microparticles made with P(CPP-SA). However, the drug release was relatively faster from P(CPP-SA) than that from P(FAD-SA) between 16 and 48 hr, and the drug release was close to 100% at 48 hr for both polymers. In spite of this slight difference, drug release was not significantly affected using these two different copolymers.

In conclusion, we have developed a simple, reproducible, and solvent-free method to produce butorphanol-loaded polyanhydride microparticles for parenteral sustained-release applications. It was found that in vitro butorphanol release can be sustained over a period of 48 hr. Also, the drug release rate from these microparticles can be modified by drug loading and size of the microparticles.

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