Sustained Local Anesthetic Release from Bioerodible Polymer Matrices: A Potential Method for Prolonged Regional Anesthesia

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Polyanhydride polymer matrices have been used successfully for sustained release of a number of drugs *in vitro* and *in vivo*. Dibucaine free base, dibucaine HCl, and bupivacaine HCl were incorporated into polymer matrices with copolymer 1,3-bis(*p*-carboxyphenoxy)propane-sebacic acid anhydride (1:4). Drug release was measured *in vitro* following incubation of the drug–polymer matrices in phosphate buffered solution, pH 7.4, at 37°C, to approximate *in vivo* conditions. Local anesthetics were released in a sustained manner yielding 90% cumulative drug release over periods ranging from 3 to 14 days. The kinetics of release varied with both the choice of local anesthetic and the method of drug incorporation into the matrix (hot melt versus compression molding). Polymer local anesthetic matrix devices (PLAM), loaded by hot melt incorporation with 20% bupivacaine, were implanted *in vivo* adjacent to the sciatic nerve in three rats. Reversible neural blockade was observed for 4 days in all animals. Polymer implants without local anesthetic showed no neural blockade. This technology could lead to methods of prolonged blockade of peripheral nerves or of sympathetic ganglia, which may be utilized for the management of postoperative pain, sympathetically maintained pain, or certain forms of chronic pain.

KEY WORDS: bupivacaine; dibucaine; local anesthetic; polymer; polyanhydride; controlled release.

INTRODUCTION

Currently, to provide regional blockade for periods longer than 1 day, clinicians must use either local anesthetic infusions via an indwelling catheter, repeated blocks, or neurolytic agents. Because the application of a controlled release local anesthetic preparation adjacent to nerves could provide a useful alternative, local anesthetics have been incorporated into liposomes and polylactic acid microspheres (1). In addition, other agents, such as methoxyflurane have been incorporated into lecithin microdroplets (2). To date, these preparations have not been widely applied in clinical or laboratory practice, and it is unlikely that either microspheres or microdroplets will be able to provide blockade for more than 3 days.

Biodegradable polymeric drug delivery systems have been used for controlled release of medications in animals and humans for days to years. A major advantage of a biodegradable controlled release system over others is that it does not require the surgical removal of the drug depleted device. Controlled-release devices have been used subcutaneously (3,4), vaginally (5), in periodontal pockets (6), near heart valves (7), and in eye and brain (8,9) with minimal adverse effects. Common drug delivery systems such as polylactic acid polymers display bulk erosion and could release potentially toxic amounts of drug during breakdown. In contrast, newer polyanhydride polymer–drug matrices erode primarily from the surface, and drug is released to the surrounding solution as layers of polymer are eroded from the surface. By altering the composition of the polyanhydride polymer matrix to be more or less hydrophobic, the release characteristics of drug from a polymer device can be adjusted. To achieve release rates predicted from previous work to be in the time frame of days to weeks (10), we copolymerized the hydrophobic monomer poly[bis(*p*-carboxyphenoxy)propane anhydride] (pCPP)[4] with a more hydrophilic monomer, sebacic acid (SA), at a 1:4 ratio.

The aim of this study is to determine if solid polyanhydride matrices can release the local anesthetics dibucaine and bupivacaine *in vitro* for days to weeks. In addition, behavioral observations were used to assess the capacity of PLAM implants to produce prolonged neural block. In comparison to liquids, solid matrices have the additional advantage of remaining at the site of implantation. For several drugs released by solid polyanhydride matrices, the *in vitro* release (pH 7.4, 37°C) adequately predicts *in vivo* release and subsequent pharmacological effects (11).

MATERIALS AND METHODS

Polymer Synthesis and Local Anesthetic Incorporation

Copolymers of CPP:SA 1:4 were synthesized as described previously (10,12). In brief, CPP and SA monomers were converted to mixed anhydrides after a 30-min reflux in acetic anhydride. The prepolymers were then recrystallized over several weeks in a mixed solvent of acetic anhydride and dimethylformamide. After melt polycondensation *in vacuo* under nitrogen sweep, the monomer ratio and purity of the copolymers were determined by decomposition in 1 *M* NaOH and UV spectrometry. For final purification, the polymer was dissolved in chloroform, precipitated in hexane, glass filtered, and rinsed with diethylether to remove free acetic anhydride. Polymers were then ground to a fine powder with mortar and pestle under liquid nitrogen to grind the polymer more easily and, after overnight lyophilization, stored dry under nitrogen gas at −30°C.

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[4] *Abbreviations used:* PLAM, polymer local anesthetic matrix; fb, free base; pCPP, 1,3bis(*p*-carboxyphenoxy)propane; SA, sebacic acid.

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Polymer local anesthetic matrices (PLAM) using dibucaine · free base (fb), dibucaine · HCl, and bupivacaine · HCl (Sigma Chemical Company, St. Louis, MO) were molded by compression or melting techniques. Crystalline drug was sieved through 150-μm pores, mixed to 5 ± 1, 10 ± 1.5, and 20 ± 2% by dry weight with polymer, and vortexed for 5 min. Tablets weighing 100–200 mg with 14-mm diameters were formed by compressing the drug/polymer mixture in a Teflon mold at 1200 psi for 8 to 10 min. Cylindrical pellets were produced by placing a tuberculin syringe filled with drug–polymer mixtures in a dry oven at 115°C for 15–20 min and then injecting the molten solid into Teflon tubing (3.2-mm i.d.). After cooling, the pellets were cut to a 1.0-cm length and then trimmed to 100 ± 5 mg. Control pellets used for *in vivo* implantation were made in the same manner as polymer without drug. All pellets were sterilized via gamma irradiation.

In Vitro Release

Since a goal of this research is to release local anesthetic from a polymer matrix *in vivo*, the buffer, pH, temperature, and sink conditions were adjusted to approximate a physiological environment for the *in vitro* release experiments. Compression tablets and hot melt pellets were incubated at 37°C in 10-mL glass scintillation vials containing Dulbecco's phosphate-buffered saline (KCl, 2.68 m*M*; KH_2PO_4, 1.47 m*M*; NaCl, 547.5 m*M*; Na_2HPO_4, 9.50 m*M*; GIBCO BRL, Gaithersburg, MD). The pH was adjusted to 7.4 with sodium hydroxide, and 15.3 m*M* sodium azide (0.1%) was added as a preservative. To approximate sink conditions in different environments, pellets were incubated in either 2- or 10-mL buffer volumes. Buffer was replaced at 0.5-, 2-, 8-, 16-, and 24-hr time points and once daily thereafter for 2 weeks to 1 month. Samples were stored at −20°C until measurement of local anesthetic concentration by spectrophotometry or HPLC. In addition, 100-mg hot melt pellets loaded 20% with bupivacaine-HCl were incubated in 25-mL buffer solutions to address release characteristics further.

Spectrophotometry

Absorption spectra, using a Hewlett Packard 8452A Diode Array Spectrophotometer and HP Vectra computer, showed dibucaine to have peaks at 252 and 328 nm. The polymer had a single peak at 255 ± 5 nm. Standard curves for dibucaine, 0–0.25 mg/mL, and polymer, 0–0.3 mg/mL, in buffer were recorded at reference (252-nm) and analytic (328-nm) absorbance (abs) wavelengths. The concentrations of dibucaine and polymer in samples were derived by solving simultaneous equations, where a, b, c, and d were constants derived from standard curves (a = 10.384, b = 0.248, c = 11.189, d = 11.035).

$$\text{Abs}_{328} = a[\text{dibucaine}] + b[\text{polymer}] \quad (1)$$
$$\text{Abs}_{252} = c[\text{dibucaine}] + d[\text{polymer}] \quad (2)$$

Samples with absorbances greater than those expected to obey the linear relationship of Beer's law were diluted 2- to 10-fold in buffer as needed. Spectrophotometry demonstrated 5.8% relative standard deviation (the standard deviation expressed as a percentage of the mean) over the range of dibucaine standards measured in triplicate.

High-Pressure Liquid Chromatography

The HPLC system developed in our lab used two Rainin pumps (HPXL, Woburn, MA) with a pressure module, Gilson 231 sample injector (Middleton, WI), Rainin Microsorb 3-μm C-18 guard (4.6 mm × 1.5-cm) and analytical (4.6 mm × 10-cm) columns, Rainin Dynamax absorbance detector (UV-D set to 210 nm for bupivacaine and 254 nm for dibucaine), and Rainin HPLC software (version 1.2) for a Macintosh IIcx. The mobile phase consisted of two solvents mixed together by isocratic differential pumping. Solvent A (pH 4.90, nonadjusted) consisted of 25 m*M* sodium acetate, 0.1% trifluoroacetic acid, and 10% acetonitrile in Baker HPLC water (Phillipsburgh, NJ). Solvent B consisted of 10% solvent A and 90% acetonitrile. Both solvents were filtered with 0.2-μm nylon, degassed with helium, and kept under 3 psi helium. Solvent A and solvent B were pumped at a 4:1 ratio to produce a mobile phase at a constant flow of 0.90 mL/min. The chromatograms showed a peak at 2.5 min for bupivacaine and at 3.7 min for dibucaine. Bupivacaine and dibucaine external standards, 0.06 to 20.0 μg, were analyzed on average after every tenth sample. The standards produced linear response values with the origin forced at zero, and the slopes equaled ~550 mV · sec · μg^{-1} for bupivacaine and ~850 mV · sec · μg^{-1} for dibucaine (R^2 values >0.995). The relative standard deviations over the range of standards measured in triplicate for both dibucaine and bupivacaine were 3.5 and 3.2%, respectively.

Statistical Analysis

Linear regression analyses were performed on the percentage cumulative release of local anesthetics and on the HPLC standards. Analysis of variance (ANOVA) with repeated measures was used to compare PLAM-leg to contralateral control-leg latencies in nerve block tests.

PLAM Implantation

Three male rats (150–250 g, Sprague–Dawley) were anesthetized with 50–75 mg/kg pentobarbital (i.p.). The shaved skin of the dorsal thigh was incised midway between the hip and the knee. The hamstring muscles were divided with a small hemostat, exposing the dorsal aspect of the sciatic nerve. Under direct vision, polymer pellets could be easily fitted into a large space between muscle layers surrounding the nerve. The space containing the pellets was bathed with 0.5 mL of an antibiotic solution (5000 U/mL penicillin G sodium and 5000 μg/mL streptomycin sulfate). The fascia overlaying the hamstrings were reapproximated with a single suture before closing skin with two wound clips. Three PLAM pellets (hot melt type loaded 20% with bupivacaine-HCl, 300-mg total) were implanted surgically along the sciatic nerve in the upper thigh, with drug-containing implants on the experimental side and control (drug-free) implants on the contralateral (control) side.

Sciatic Nerve Block

Utilizing a technique developed in this lab, sensory

blockade was measured by the time required for each rat to withdraw its hind paw from a 56°C plate (IITC Life Science Instruments, Model 35-D, Woodland Hills, CA). The rats were held with a cloth gently wrapped above their waist to restrain the upper extremities and obstruct vision. The rats were positioned to stand with one hind paw on a hot plate and the other on a room temperature plate. With a computer data collection system (Apple IIe with a footpad switch), latency to withdraw each hind paw to the hot plate was recorded by alternating paws and allowing at least 15 sec of recovery between each measurement. If no withdraw occurred from the hot plate within 15 sec, the trial was terminated to prevent injury and the termination time was recorded. Testing ended after five measurements per side, the high and low points were disregarded, and the mean of the remaining three points was calculated for each side. The animals were pretested for at least 1 week before PLAM implantation to reduce variability in their leg withdrawal response.

Motor block was assessed by observation of leg and paw function just prior to leg-withdrawal measurements from a hot plate. The rat's ability to walk on a waxed tile floor and toe splay in response to being lifted by the tail was rated. Animals were handled in accordance with institutional, state, and federal guidelines.

RESULTS

In Vitro Release

Dibucaine · fb incorporated into 200-mg PLAM tablets by compression molding was released linearly ($R^2 > 0.975$) for 7 days into 2-mL vol of buffer as measured by spectrophotometry (Fig. 1A). The amount of drug released was plotted cumulatively and expressed as a percentage of the total drug released, whereas total release is defined as the asymptote of the release curve (i.e., <0.05 mg/day released). The 5 and 10% drug-loaded tablets released drug linearly from the start, whereas the 20% tablet achieved greater linearity after the first 12 hr ($R^2 = 0.969$ compared to $R^2 = 0.985$ after 12 hr). By the seventh day, 5% tablets (~200 mg) released dibucaine · fb, a total of 3.5–5.2 mg, 10% tablets released 9.6–12.6 mg, and 20% tablets released 26.0–26.8 mg. By day 15, dibucaine · fb release rates were less than 0.1 mg/day for all tablets. The cumulative release curves of duplicate tablets, expressed as the percentage of total drug released, did not differ at any time point by more than 10, 5, and 2% for tablets containing 5, 10, and 20% dibucaine · fb, respectively.

In comparison, under similar release conditions in 2 mL of buffer, 40–60% of the dibucaine · HCl was released from ~200-mg tablets within the first day and approached linearity ($R^2 > 0.992$) from day 2 to day 7 (Fig. 1B). By the seventh day, the 5% tablet released a total of 4.9 mg, the 10% tablet released 10.6 mg, and the 20% tablet released 25.9 mg. By day 15, dibucaine · HCl was released at rates less than 0.1 mg/day.

Duplicate 100-mg compression-molded tablets containing 20% dibucaine · fb, released in 10-mL buffer solutions and measured by both HPLC and spectrophotometry, released 85% of drug (17.0 mg) linearly ($R^2 > 0.957$) within the first 2 days (Fig. 2A). Compared to dibucaine · fb, the dibucaine · HCl in 100-mg compressed tablets was released at a much faster rate, with >75% of drug being released within 12 hr. Hot-melted pellets containing either 20% dibucaine · fb or dibucaine · HCl released 90% of drug (18.0 mg) in a linear fashion ($R^2 > 0.999$ for fb, $R^2 > 0.994$ for HCl) over the first 4 days (Figs. 2A and B). Individual data points for duplicate tablets showed small differences from the mean (<6% compressed-dibucaine · fb, <4% hot melted-dibucaine · fb, <8% compressed-dibucaine · HCl, and <3% hot melted-dibucaine · HCl).

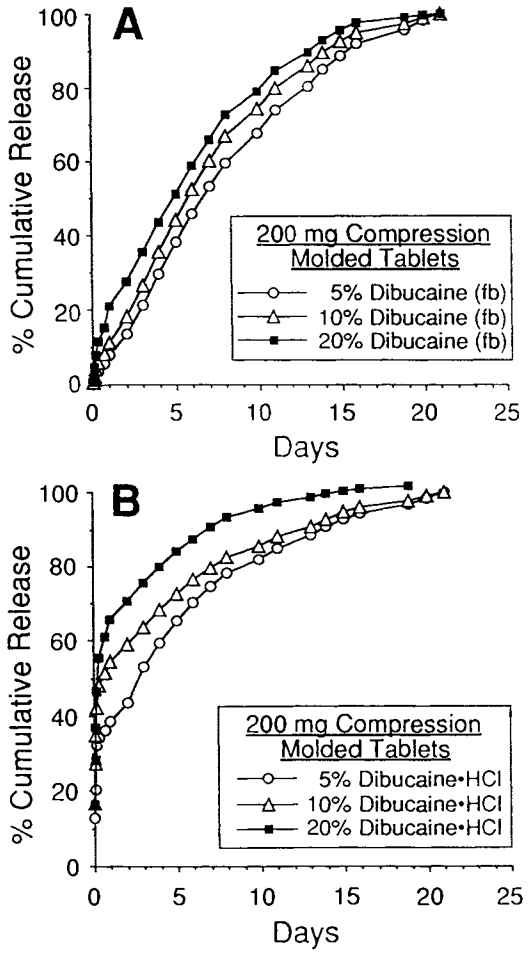

Fig. 1. Ten, twenty, and forty milligrams of dibucaine · fb (A) and dibucaine · HCl (B) were incorporated in 200-mg compression-molded tablets and placed in 2.0-mL buffer volumes. Cumulative release of dibucaine · fb represents the means of duplicate tablets (see Results for variation), whereas dibucaine · HCl tablets were run in singlet. The drug concentration in the releasates was measured by spectrophotometry.

Hot melted-pellets (100 mg) made with bupivacaine · HCl (20 mg) released 90% of the drug (18 mg) linearly ($R^2 > 0.991$) up to 5 days, while the tablets released 90% within 2 days, in 10-mL buffer solutions (Fig. 2C). In 25-mL buffer solutions, 100-mg hot melt-pellets made with 20 mg bupivacaine-HCl released drug linearly ($R^2 > 0.990$ for duplicate pellets using HPLC) up to 5 days at a faster rate in comparison to that found in both the 10-mL buffer solutions (~1.4–1.9% greater cumulative release per day) and the

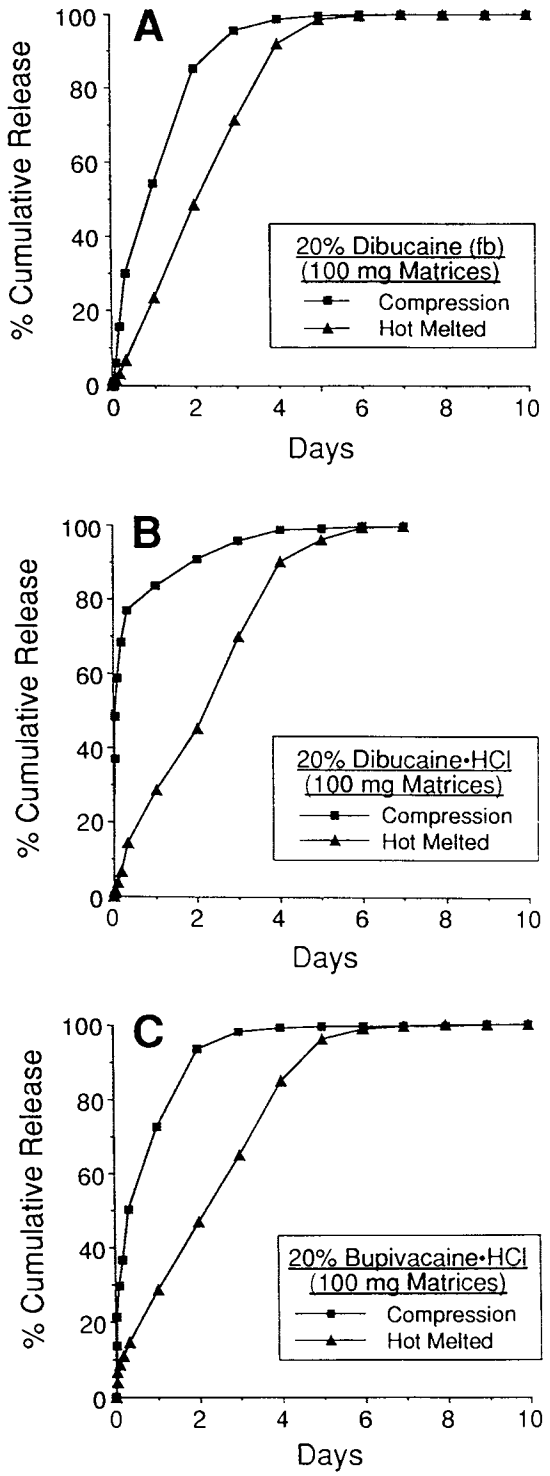

Fig. 2. Twenty milligrams of dibucaine · fb (A), dibucaine · HCl (B), and bupivacaine · HCl (C) were incorporated into 100-mg devices by either compression or hot-melt molding. Cumulative release curves represent means of duplicate tablets (see results for variation). Dibucaine · HCl and bupivacaine · HCl concentrations in buffer volumes of 10.0 mL were measured by HPLC. Dibucaine · fb concentrations were measured by both HPLC (data shown) and spectrophotometry (data not shown; see Materials and methods).

2-mL buffer solutions (~4.2–5.5% greater cumulative release per day). The cumulative release of duplicate bupivacaine · HCl tablets and pellets did not differ by more than 7% per sample at each time point.

Spectrometry vs HPLC

Spectrophotometric measurements gave absolute values that were less than those obtained by HPLC (average difference of 0.14 ± 0.07 mg · mL^{-1} · day^{-1}, mean ± SD) for dibucaine · fb in 10-mL releasates from 100-mg devices. The HPLC values more closely corresponded to the expected cumulative release than spectrophotometry, as predicted by the known amount of drug incorporated into the devices. Perhaps the error in the spectrophotometric measurements is caused by variations in the polymer standard curves and the interference of large concentrations of polymer with low concentrations of dibucaine. However, spectrophotometry and HPLC gave similar values for the cumulative release profile of dibucaine, indicating that the error in spectrophotometry was constant for all samples. To assess drug release further, after termination of the assay each device was immersed three times in 20 mL distilled water for 30 min, freeze-dried for 48 hr, and then weighed. In all cases polymer weight approximated the release of drug (±5–10%), that is, the postrelease weight of each device approximated the weight of the polymer matrix without drug after normalizing for polymer loss from degradation or crumbling (i.e., size measurements).

Neural Block

In all rats, various levels of sensory and motor block was observed for up to 5 days postimplantation of the PLAM pellets loaded 20% with bupivacaine. Leg withdrawal latency to heat was increased above baseline levels for postimplantation days 1–4 [$F(1,18) = 34.03$, $P < 0.0001$] and not for postimplantation days 6–9 [$F(1,18) = 1.20$, $P = 0.29$]. Since two animals still showed some signs of neural block on postimplantation day 5, this day was not included with statistical analysis of days that show animals returning to base-

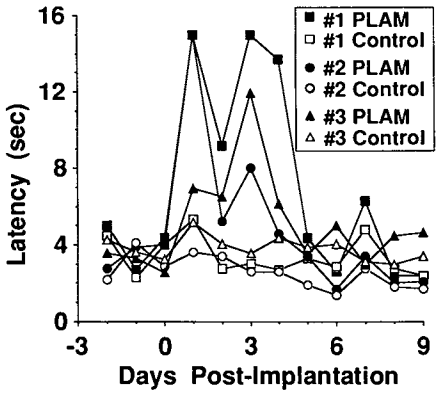

Fig. 3. This graph shows individual data from three rats in leg-withdrawal latency tests 3 days before and 9 days after PLAM implantation. Each rat received bilateral implants (hot melt) adjacent to the sciatic nerve, three 100-mg PLAM implants loaded with 20% bupivacaine in one leg, and three 100-mg polymer implants without drug in the contralateral control leg.

line. All rats returned to baseline levels by day 6 (Fig. 3). The rats showed signs of motor block for the first 2–3 days post-implantation with clubbing of the paw at 24 hr and inability to splay their toes properly at day 2 and 3. By day 4 there were no signs of motor deficits. In all rats, the control leg never showed any sign of motor or sensory block.

DISCUSSION

Local anesthetics can be successfully incorporated into pCPP:SA (20:80) and released in a controlled manner for periods of up to 2 weeks. We found that the rate of local anesthetic delivered *in vitro* is dependent on several factors including the hydrophobicity of the drug, the ratio of drug to polymer, the method of drug incorporation, the mass and surface area of the device, and the releasate volume. These results are consistant with previous release studies using the same copolymer matrix impregnated with other drugs (10).

Compared to the dibucaine · fb incorporated by compression molding, the hydrochloride form shows a much higher rate of initial release, with 40–60% released within the first day (Fig. 1). Because the hydrochloride form is very soluble, small portions of drug lying on the surface will immediately be released into the solution. Furthermore, fast erosion of drug from the surface will result in channels that allow the solution to penetrate deeper layers of the matrix and release more drug. In comparison, the more hydrophobic dibucaine · fb will tend to remain within the matrix, causing its release to be more dependent on polymer erosion and, therefore, obeying zero-order kinetics (10). Because the free-base form of dibucaine is less soluble than the HCl form, it is possible that saturation effects rather than polymer surface erosion may, in part, account for the difference in release kinectics between the two forms. Compression-molded tablets containing bupivacaine · HCl also show a fast initial release (69–75% within the first day).

Unlike compression-molded tablets, pellets made by the hot-melt procedure do not release large amounts of dibucaine · HCl during the first day of incubation (Fig. 2). The release kinetics of the HCl and free-base forms of dibucaine are similar, within experimental error. Perhaps hot-melting techniques are similar to injection molding (10), creating more dense and more homogeneous matrices and, therefore, releasing drug more linearly than compression-molded matrices, independent of form of drug. These findings demonstrate that the difference in solubility between dibucaine-free base and dibucaine-HCl does not affect polymer erosion and drug release from hot-melt pellets.

The amount of local anesthetic released per day increased proportionately with the percentage of drug incorporated into the matrix (from 5 to 10 to 20%). In addition, the rate of cumulative release, expressed as a percentage of total drug released, also increased with greater drug/polymer ratios. At local anesthetic/polymer ratios greater than 20%, the fragility of the matrix increases. For this reason, we did not use polymer matrices with greater than 20% drug incorporated.

Both the surface-to-mass ratio of the drug/polymer matrix and the releasate volume will effect the erosion of polymer layers and the release of drug (10). Greater than 80% of dibucaine · fb was released from 100-mg compression-molded tablets in 10-mL buffer solutions within 2 days, compared to 7 days for 200-mg tablets in 2-mL buffer solutions (replacing buffer at 0.5, 2, 8, 16, and 24 hr, then once daily thereafter). Drug release was expected to be maximal under sink conditions with 25-mL buffer solutions, close to maximal in the 10-mL buffer solutions, but retarded in the 2-mL buffer solutions (10). Further, 2-mL releasates allowed us to ensure concentrations of drug measurable by spectrophotometry, and to explore the kinetics of release under nonideal conditions, which may simulate *in vivo* conditions that include encapsulation and slow fluid movement. *In vivo* implantation areas containing high blood flow or large fluid volumes are better approximated *in vitro* by 10- and 25-mL volumes of collection buffer.

We have shown that small 100-mg devices, hot melted with dibucaine · fb, dibucaine · HCl, and bupivacaine · HCl, can be used to deliver local anesthetic at rates above 3.5 mg/day for over 4 days with zero-order kinetics. We show, by manipulating the percentage drug incorporated, the form of local anesthetic (fb vs HCl), the method of production (compression vs hot melt), and the shape of the matrix, that it is possible to tailor a system to deliver a specified dose. When applied *in vivo*, anatomic barriers will limit the maximum mass and number of pellets implanted, while areas of low perfusion may retard release. Otherwise, the *in vitro* kinetics of local anesthetic release is expected to be an approximate indicator of regional *in vivo* action.

Preliminary *in vivo* studies suggest that this technology may be used to provide prolonged regional analgesia (13). Indeed, the present preliminary findings show that PLAM implants along the sciatic nerve can produce neural block for 4 days. Detailed *in vivo* studies are in progress to assess the behavioral, biochemical, and histological effects of timed-release nerve blockade in rats. Potential applications for PLAM technology may include blockade of peripheral nerves during surgery, particularly in dermatomes for which protective sensation is unimportant, such as intercostal blockade for thoracotomy. Similarly, longer acting forms of this preparation may permit a convenient approach to lumbar sympathetic blockade.

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