A ONE-WEEK SUBDERMAL DELIVERY SYSTEM FOR L-METHADONE BASED ON BIODEGRADABLE MICROCAPSULES

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Microspheres containing 13–16% L-methadone were prepared from three biodegradable polymers, poly(L-lactic acid), PLLA; poly(glycolic acid-co-L-lactic acid), PGLA; and poly(ε-caprolactone-co-L-lactic acid), PCL-LA, using the solvent evaporation method. The release of L-methadone from microspheres of PCL-LA (75–85 mol% L-lactic acid) was complete within 48 hours. Release from PGLA (80 mol% L-lactic acid) microspheres was almost as rapid, but 20% of the drug remained in the polymer matrix. Release from PLLA microspheres was subject to a 3–4 day induction period prior to loss of the drug over the next 5 days. This induction period for PLLA and the immediate release of L-methadone from PGLA microspheres were the result of an exceptionally large acceleration of the hydrolytic chain cleavage of the polymers in the presence of the basic drug. Measurements of the diffusion coefficients of L-methadone in the three polymers showed that only in the case of PCL-LA was Fickian diffusion responsible for the observed kinetics. Both blending and changes in the copolymer composition could be used to control the permeability and the induction period associated with L-methadone release from microspheres. It was possible to achieve zero-order release of L-methadone for six days by combining microspheres prepared from three different polymer compositions. Application of the Wurster process afforded polymer-coated L-methadone crystals (i.e., microcapsules) with an 80% drug loading.

INTRODUCTION

The therapeutic effectiveness of the methadone treatment program, begun in 1964 by Dole and Nyswander, is now well documented [1,2]. Methadone, when provided as a daily dose, has functional effects quite different from those of injected heroin, morphine, and other narcotics. Participants in this program lose their craving for narcotics and are able to resume normal lives. Nevertheless, a significant proportion of failures occur and have been attributed to mixed drug abuse, lack of supporting modalities, side effects, fluctuations in plasma levels, and the inconvenience of daily visits to the clinic [3–5]. L-α-Acetylmethadol (LAAM) has been studied as a long-acting substitute which is reported to be more acceptable to some subjects, in part because of the reduction of clinical visits to three times per week [6]. The appeal of reducing clinical visits, while still avoiding problems of patient compliance and drug diversion, coupled with the potential for reducing the dose, provide a strong justification for developing a subdermal controlled delivery system for L-methadone.

A number of studies have considered the optimum dose of methadone for the maintenance
of heroin addicts [7-9]. It is reported that the minimum oral dose of DL-methadone is 30 mg/day, while results have been more consistent with a dose of at least 60 mg/day because of subject variability of the metabolism rate. The best record of rehabilitation was achieved when the plasma level was greater than 200 ng/ml [8]. There is no information on the extent to which the dose might be reduced when administered subdermally on a continuous basis, to produce an invariant plasma concentration. This factor, plus the use of L-methadone in place of the racemate, suggest that a release rate of 30 mg/day or less may be sufficient.

A release rate of 30 mg/day is substantially higher than has been achieved previously using transdermal or subdermal polymeric controlled delivery systems. This rate can be achieved potentially with microcapsules. Microcapsules provide for ease of injection, while their high surface-to-volume ratio maximizes permeability and surface erosion. The size of the dose dictates the frequency of administration of a formulation be at least every 1 to 2 weeks, in order to limit the bulk of the injection to an acceptable size.

Three polymers were selected for study: poly(ε-caprolactone-co-L-lactic acid), PCL-LA; poly(L-lactic acid), PLLA; and poly(glycolic acid-co-L-lactic acid), PGLA. The copolymer PCL-LA is a rubbery polymer with relatively high permeability [10]. It is subject to rapid hydrolytic chain cleavage, with a short induction period before the onset of bioerosion [11]. PGLA is a less permeable but more rapidly degraded polymer that has frequently been used in microcapsule formulations [12]; it is commonly assumed but not proven that bioerosion is responsible for drug release. PLLA is of interest because it has been used to prepare microporous membranes [13] and in at least one case high drug release rates observed using microcapsules of this polymer have been attributed to diffusion through pores rather than to classical Fickian diffusion [14].

**EXPERIMENTAL SECTION**

**Polymer synthesis and characterization**

PLLA, PGLA, and PCL-LA were prepared by bulk polymerization of the redistilled (ε-caprolactone) or recrystallized (L-dilactide, diglycolide) lactones at 140°C for 18 h in an evacuated glass vessel in the presence of stannous octoate [11]. The polymers were purified by precipitation from methylene chloride with methanol and then dried *in vacuo*.

Copolymer compositions were determined by 1H-NMR spectroscopy using a Bruker Model WM-250 Supercon spectrometer with samples dissolved in CDCl₃. Molecular weights were determined by gel permeation chromatography (GPC) in chloroform using a set of five μStyr- agel columns (Waters Assoc.) with nominal pore sizes of 10⁶, 10⁵, 10⁴, 10³, and 50 nm, and a flow rate of 1 ml/min. The GPC traces were evaluated by the universal calibration method [15] using polystyrene standards (Waters Assoc., Ventrion) and published Mark Houwink constants for PGLA [16] and PLLA [17]; the constants for PCL-LA, ≥75 mol% L-lactic acid, were assumed to be the values reported for PLLA. The molecular weights of the polymers used are indicated in Table 2 and Fig. 5. Polymer and L-methadone crystallinities were determined by differential scanning calorimetry using a Perkin-Elmer Model DSC-2 instrument, a heating rate of 10–20°C/min, and an indium standard. The heat of fusion of pure L-methadone was determined by DSC to be 23.8 cal g⁻¹. The Tg values of the polymers were derived from their softening points, measured using a Perkin-Elmer thermomechanical analyzer (TMA) and a heating rate of 5–10°C/min.

The diffusion coefficients and maximum steady-state flux of L-methadone in the polymers were determined at 37°C using a standard diffusion cell with two thermostated compartments separated by the polymer membrane. Each compartment was stirred magnetically. The downstream compartment contained
phosphate buffer, pH 7.4, while the upstream compartment contained solid drug and was maintained at a known pH near to the pKₐ of L-methadone with a borax buffer. The L-methadone concentration in the upstream compartment was calculated using a pKₐ of 9.52 [18].

**Preparation of microspheres and microcapsules**

Microspheres were prepared by the solvent evaporation method at ambient pressures. Typically, a solution of the polyester (300 mg) and L-methadone (60 mg) in CH₂Cl₂ (4 ml) was poured rapidly into 20 ml of water containing 0.4 wt% of poly(vinyl alcohol). The mixture was stirred vigorously with a magnetic stirrer to form an emulsion; stirring was then continued at 37°C until the CH₂Cl₂ had evaporated. The microspheres were separated, washed with deionized water, and dried in vacuo. The dried microspheres were size-separated by sieving and stored at 0°C until used. Microcapsules were prepared by an air suspension coating procedure by Biotek, Inc., Woburn, MA.

The L-methadone content before and after release rate measurements was determined by dissolving a weighed quantity of microspheres or microcapsules (about 10 mg) in spectral grade CHCl₃ (2 ml). The UV absorbance at 295 nm was determined and, after correcting for polymer absorbance, the L-methadone content was calculated from a standard curve of absorbance versus L-methadone concentration.

The size and surface characteristics of the microcapsules and microspheres before and after release rate studies were determined by scanning electron microscopy (SEM) using an ETEC model B-1 Autoscan microscope.

**Release rate measurements**

Approximately 20 mg of microcapsules or microspheres were placed in a dialysis bag containing 0.04 M phosphate buffer, pH 7.4. This bag was immersed in 120 ml of the same buffer, and maintained at 37°C in a shaker bath. The release of L-methadone into the aqueous reservoir was determined by spectrophotometric assay of aliquots at 220 nm. The concentration of L-methadone was calculated from a standard curve of L-methadone in 0.05 N hydrochloric acid. Release rates are reported as the mean of duplicate measurements; the deviation of each data point from the mean value for duplicate experiments was generally no greater than ±5%.

**RESULTS AND DISCUSSION**

Microspheres containing 13–16% L-methadone were prepared from each polymer by the solvent evaporation technique [19], using poly(vinyl alcohol) as the surfactant. The microspheres were size-separated by sieving and verified to be defect-free spheres by SEM (Fig. 1). No L-methadone crystallinity was detected by DSC, indicating that at this concentration the drug existed as a solid solution [20,21]. Microcapsules were prepared by spray-coating L-methadone crystals using fluidized bed (Wurster) equipment, to obtain a higher drug loading, and minimize the size of the formulation for clinical application. With PCL-LA as the polymer, an 80% drug loading was achieved. DSC showed that, based on the observed heat of fusion, the methadone incorporated by this technique was 90% crystalline.

The rate of release of L-methadone from each preparation was determined in vitro at 37°C. The effects of using reservoirs of (a) unbuffered deionized water and (b) phosphate-buffered water, pH 7.4, were compared in initial experiments. The rate of release from PCL-LA microcapsules into an unbuffered aqueous reservoir was zero order and much slower than when a pH 7.4 buffered reservoir was used (Fig. 2). L-Methadone, a weak base (pKₐ 9.52) [18], is only partially protonated in nonbuffered water. The lower, zero-order kinetic profile observed with the unbuffered sink can thus be at-
tributed to the low water solubility of \( \text{L}-\text{methadone} \), reflected by its lipophilicity (\( \log P_{\text{water}} = -4.19 \)) [18], which causes the aqueous boundary layer at the polymer–water interface to become rate limiting. The use of a buffered reservoir, pH 7.4, results in essentially complete protonation of \( \text{L}-\text{methadone} \) in the aqueous phase, reducing the thermodynamic activity of the drug at the polymer–water interface to zero and maximizing the drug concentration gradient. All subsequent measurements were conducted using pH 7.4 buffer.

The rates of release of \( \text{L}-\text{methadone} \) from comparable sized microspheres of PCL-LA, PGLA, and PLLA are shown in Fig. 3. The rates of release from PGLA and PCL-LA microspheres were both very rapid, although only 80–90% of the \( \text{L}-\text{methadone} \) was released from the PGLA microspheres. The incomplete release of drug from polyester microspheres is not without precedent [22]. In contrast to the immediate and rapid release of \( \text{L}-\text{methadone} \) from PCL-LA and PGLA microspheres, no drug was released from PLLA microcapsules for 3–4
Fig. 3. In vitro release of L-methadone from microspheres of (□) PCL-LA, 50–212 μm, (◇) PGLA, 106–212 μm, and (■) PLLA, 106–212 μm. Reservoir: 0.04 M phosphate buffer, pH 7.4.

days; at this time drug release became rapid and 80% was released in an additional five days before the rate slowed. Scanning electron microscopy (SEM) showed the drug-depleted PLLA microspheres were largely unchanged in size and surface characteristics (Fig. 4). There was some evidence of surface erosion but no visible pores or catastrophic defects that might explain the sudden, delayed onset of rapid L-methadone release.

A partial understanding of the mechanism of L-methadone release was provided by measurement of the diffusion coefficients ($D$) of L-methadone in the three polymers. The diffusion coefficient of L-methadone in PCL-LA (75% LA), determined by the lag time method [23], was $6.28 \pm 0.24 \times 10^{-11} \text{cm}^2 \text{s}^{-1}$. This is significantly smaller than the value of $7.67 \pm 0.92 \times 10^{-10} \text{cm}^2 \text{s}^{-1}$ determined for poly(ε-caprolactone), reflecting the high proportion of the less mobile (glassy) lactate sequences in the PCL-LA. It has previously been demonstrated that increasing the proportion of lactate in ε-caprolactone–lactic acid copolymers produces a systematic increase in the $T_g$ [10]. Using the experimental value of $D$ for PCL-LA, a mean microsphere radius ($R$) of 50 μm, and the expression for fractional release ($M_t/M_\infty$) of a dissolved drug from a spherical matrix (eqn. 1) [23], the calculated time for 60% release

$$M_t/M_\infty = 1 - \frac{6}{\pi^2} \exp \left( -\frac{\pi^2 D t}{R^2} \right)$$

for $M_t/M_\infty > 0.6$

from a sphere containing dissolved drug is 2.4 days. This calculated value is not inconsistent with the observed time of 1 day because of the additional contribution of plasticization of the polymer by the large amount of drug dissolved in the microspheres. The $T_g$ values of PCL-LA (75% LA) microspheres with and without methadone were determined by measurement of the softening points using thermomechanical analysis. The results are summarized in Table 1 and show a small but measureable plasticization by the drug.

No flux of L-methadone through membranes of PGLA and PLLA could be detected and, based on the sensitivity of the experimental method, it was estimated that the drug flux in these polymers was at least 100 times less than in PCL-LA. That is, Fickian diffusion was not the primary mechanism of release of L-methadone from PGLA and PLLA. The $T_g$ values of PLLA and PGLA microspheres were depressed by L-methadone, although the decrease in the case of the latter polymer was not statistically significant (Table 1).

GPC measurements of polymer molecular weights during the period of the drug release (Table 2) demonstrated that the release of L-methadone from PLLA and PGLA microspheres was primarily associated with degradation of the polymer. Very rapid chain scission of PGLA was observed during the 24–48 h of L-methadone release, while a slower rate of molecular weight decline was observed with PLLA. Degradation of both polymers in the absence of L-methadone was very much slower (Fig. 5). These accelerated rates, greater than 100 fold in the case of PLLA, must be attributed to general base catalysis of the hydrolysis of the po-
Fig. 4. Scanning electron micrographs of (a) PGLA and (b) PLLA microspheres, size range 106-212 µm, after release of the drug. Magnification: 400× (PGLA); 60× (PLLA).

Table 1

The glass transition temperatures of PCL-LA, PGLA and PLLA microspheres before and after incorporation of L-methadone (15 wt-%)

<table>
<thead>
<tr>
<th></th>
<th>PCL-LA (75%)</th>
<th>PLLA</th>
<th>PGLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without L-methadone</td>
<td>7.4 (±0.4)</td>
<td>32.6 (±9.8)</td>
<td>36.1 (±5.2)</td>
</tr>
<tr>
<td>With L-methadone</td>
<td>12.9 (±1.8)</td>
<td>40.2 (±3.0)</td>
<td>32.4 (±3.5)</td>
</tr>
</tbody>
</table>

Polymeric ester linkages by the tertiary amino function of L-methadone. This result was unexpected in view of an earlier failure to observe base-catalyzed hydrolysis of PLLA in the presence of triethylamine [16]; it can be rationalized as the result of the relatively high concentration (15%) of the basic drug in the polymer achieved by the solvent evaporation method of microencapsulation. Similar but much less dramatic examples of the base-promoted degradation of PLLA microcapsules have been published recently [24-27]. The L-methadone which is retained in the microspheres appears to represent that fraction of the amine which is protonated by the carboxyl end groups of the partially hydrolyzed low molecular weight polyester.

Both the small diffusion coefficient and the induction period before L-methadone is released from PLLA microspheres are inconsistent with classical Fickian diffusion from a semi-permeable polymer. Rather, it appears that the induction period can be equated with the time required for the PLLA to achieve a critical low molecular weight. In support of this relationship between the induction period and polymer molecular weight, there was no induction period when microspheres were prepared from low molecular weight PLLA, $M_w$ 1500. The release of steroids and peptides from PGLA provides a precedent for biphasic kinetic behavior and its molecular weight dependence [28,29]. Clearly, the ability to observe an induction period is dependent on the initial molecular weight and rate of degradation of the polymer, relative to the timeframe of the experiment. Previous examples were limited to PGLA because of the rapid
TABLE 2

L-methadone-promoted degradation of polymer during the time period of the drug release

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Methadone (%)</th>
<th>Size (µm)</th>
<th>Molecular weight ($M_\text{w}$)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 day</td>
</tr>
<tr>
<td>PLLA</td>
<td>15.4</td>
<td>212-500</td>
<td>106700</td>
</tr>
<tr>
<td>PGLA</td>
<td>14.3</td>
<td>106-212</td>
<td>23100</td>
</tr>
<tr>
<td>PCL-LA</td>
<td>13.8</td>
<td>50-200</td>
<td>73500</td>
</tr>
<tr>
<td>PCL-LA</td>
<td>80.5</td>
<td>150-212</td>
<td>11500</td>
</tr>
</tbody>
</table>

Fig. 5. $M_\text{w}$ change of microspheres during the time period of the drug release; (♀) PLLA (15.4% initial L-methadone drug content), (+) PGLA (14.3% initial L-methadone drug content), (◇) PCL-LA (13.8% initial L-methadone drug content), (□) PLLA (no drug), and (■) PGLA (no drug).

rate of chain cleavage of this hydrolytically unstable polymer. In the present system, the degradation of PLLA is accelerated to the point that an induction period is observed within the time period of the experiment. With PGLA in the presence of L-methadone, the degradation is sufficiently rapid that the induction period is too short to be observed.

Once the critical molecular weight is attained, the mechanism of drug release from PLLA and PGLA may be a combination of polymer surface erosion and drug diffusion. Diffusion coefficients are expected to increase as the molecular weight and chain entanglement of a polymer decreases, although this effect is not well documented [30]. In at least one case, the concurrent loss of $^{14}$C-labeled polymer and drug suggests that polymer erosion is partially responsible for drug release [27].

When PCL-LA was formulated as microcapsules, both the rate of release of L-methadone (Fig. 2) and the decrease in the molecular weight of the polymer (Table 2) were lower than the rates observed with PCL-LA microspheres. The reduced rate of polymer degradation is consistent with a lower concentration of L-methadone in the polymer wall of the microcapsules, which reduces the base catalyzed rate of chain scission.

Control of L-methadone release rates

Two methods of manipulating the kinetics of L-methadone release were studied: modification of the comonomer composition of PCL-LA to achieve a reduced polymer permeability, and blending of PGLA, PCL-LA and PLLA in different proportions as a means of controlling the rate of hydrolytic chain scission, and hence the induction period and onset of drug release rate. The ability to control both the permeability and biodegradability of copolymers of ε-caprolactone and lactic acid by changing the monomer ratio has been described previously [10]. There is also a growing body of data which demonstrates that transport of gases and low molecular solutes in blends of polymers can be
Fig. 6. *In vitro* release of L-methadone from microspheres prepared from different copolymers of ε-caprolactone and L-lactic acid: (■) 75 mol% LA, (◇) 85 mol% LA, (+) 95 mol% LA, and (□) 100 mol% LA. The medium was pH 7.4 phosphate buffer, 37°C.

...changed systematically with the blend composition, regardless of whether the blends are compatible [31].

Increasing the L-lactic acid content of PCL-LA led to a decrease in L-methadone release rate, reflecting the increasing contribution of glassy, impermeable lactate sequences. The diminution of the release rate was not great in the range of LLA:CL ratios of 75:25 to 85:15 mol–mol%. However, as the ratio was increased to 95:5 mol–mol%, the rate of L-methadone release slowed and began to assume the profile observed with PLLA microspheres, albeit with a shortened induction period of approximately 24 h (Fig. 6). A similar result was achieved by preparation of microspheres from blends of PLLA and PGLA (Fig. 7).

Different results were obtained when blends of PCL-LA and PLLA were used to prepare L-methadone microspheres. With ratios of PLLA to PCL-LA in the range of 1:1 to 2:1 wt–wt%, there was no induction period but the kinetics were biphasic. The rate was rapid initially, but then decreased significantly after approximately 50% of the drug was depleted (Fig. 8). This behavior was accentuated as the PLLA proportion in the blend was increased, until the kinetics assumed the profile characteristic of PLLA microspheres.

While none of the blends or copolymer com-

Fig. 7. *In vitro* release of L-methadone from microspheres of (■) PGLA, (◇) a 1:1 wt–wt% blend of PGLA and PLLA, and (□) PLLA. The medium was pH 7.4 phosphate buffer, 37°C.

Fig. 8. *In vitro* release of L-methadone from microspheres of (■) PCL-LA, (×) blends of PCL-LA:PLLA (1:1 wt–wt%), (◇) PCL-LA:PLLA (1:1.73 wt–wt%), and (□) PLLA. The diffusion medium was pH 7.4 phosphate buffer, 37°C.
positions provided the one week zero-order kinetics which were required for L-methadone maintenance therapy, it appeared possible that this might be achieved with a combination of compositions. The kinetics of L-methadone release from a 1:1 mixture of PLLA microspheres and PCL-LA (95% LA) microspheres were almost zero order but for the retention of a short induction period (Fig. 9a). This induction period was eliminated by inclusion of microspheres of the more permeable copolymer PCL-LA (85% LA). A 11:48:41 mixture of microspheres of PCL-LA (85% LA), PCL-LA (95%), and PLLA provided zero-order kinetics for a six-day period, in good agreement with the rate calculated from the weighted sum of the kinetics of the individual polymers (Fig. 9b).

The in vivo evaluation of the various formulations is now in progress.

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