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RESEARCH PAPER

Development of Biodegradable Drug Delivery System to Treat Addiction

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ABSTRACT

Opiate addiction is a serious problem that has now spread worldwide to all levels of society. Buprenorphine has been used for several years for the treatment of opiate addiction. The objective of this project was to develop sustained-release biodegradable microcapsules for the parenteral delivery of buprenorphine. Biodegradable microcapsules of buprenorphine/poly(lactide-co-glycolide) were prepared using two main procedures based on an in-water drying process in a complex emulsion system. These procedures differ in the way the organic solvent was eliminated: evaporation or extraction. The effect of drug loading and the effect of partial saturation of the aqueous phase with the core material during the in-water solvent evaporation were also studied. The efficiency of encapsulation increased from 11% to 34% when the drug loading was decreased from 20% to 5%. There was no significant change in the efficiency of encapsulation when the aqueous phase was partially saturated with buprenorphine. In changing the solvent removal process from evaporation to extraction, no significant change in the efficiency of encapsulation was observed. The microcapsules prepared by the solvent evaporation were smooth and spherical. However, the microcapsules prepared by the extraction of the organic solvent lost their surface smoothness and became slightly irregular and porous compared with the other batches. The average particle size of the microcapsules was between 14 and 49 μm. The cumulative drug release was between 2% and 4% within the first 24 hr. A sustained drug release continued over 45 days.

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INTRODUCTION

A rational approach to the development of a therapeutic program for the treatment of opiate addiction requires the use of antiaddictive drug over an extended period of time (1). The antiaddictive drugs used over the decades are narcotic agonists and/or antagonists, which generally have chemical structures similar to those of opiates (2). For several years, methadone and naltrexone have been used for the treatment of opiate-dependent individuals (3,4). Buprenorphine is the other promising drug being tested for opiate maintenance programs (5–8).

Buprenorphine is a highly lipophilic partial μ-opiate agonist. It has been used several years for the treatment of drug addiction. Addicts given buprenorphine rapidly reduce the self-administration of intravenous heroin (5,9). Buprenorphine has two important advantages over the opiate agonist methadone as a pharmacotherapeutic agent for opiate addiction: (*a*) it does not induce significant physical dependence in humans, and (*b*) the possibility of lethal overdose is minimum due to its opiate antagonist properties (9–11). This drug thus would be a suitable candidate for an opiate maintenance program (12). Buprenorphine appears to have a much lower dependence liability than morphine (8). The opiate agonist component of buprenorphine that raises concern about its potential addiction liability constitutes its primary advantage over treatment with the opiate antagonist naltrexone. The opiate agonist component of this mixed agonist-antagonist drug is important for patient acceptance since naltrexone, an equally potent narcotic antagonist, has not been widely effective in the treatment of heroin addiction. It has been very difficult to retain heroin addicts in naltrexone treatment programs (11,13,14). A parenteral preparation containing 0.3 mg of buprenorphine in 1 ml is presently available on the market. A new formulation of buprenorphine needs to be developed for the opiate maintenance program (15).

Sustained-release preparations that block narcotic receptors for about a month will have an advantage over the current oral preparations, which require dosing daily or three times a week (16,17). Moreover, during oral dosing, the patient is frequently confused by the decision whether to continue or discontinue the treatment. To avoid this confusion, it is desirable to develop a sustained-release formulation that could be implanted subcutaneously so that removal could only be carried out by a physician and not by the patient. Thus, the development of a biodegradable implant system capable of maintaining a therapeutically useful plasma concentration of narcotic agonist and/or antagonist is recognized as an important area of research (18). The most widely investigated biodegradable polymers are aliphatic polyesters based on lactic acid and glycolic acid. The copolymers of these two have attracted much attention because the biodegradation rate of the copolymer is easily controlled by altering the composition (19). These polymers have been used with numerous drugs and have been shown to be biocompatible (18,20–22). Although several narcotic agonists and/or antagonists, including naloxone, methadone, and cyclazone, have been used with lactide homopolymers and lactide/glycolide copolymers, most reports published used the combination of these copolymers and naltrexone (3,23,24). However, biological incompatibility of naltrexone precludes the use of this drug as a biodegradable implant.

Considering only the classical methods of drug administration, one would be forced to search for compounds that have significantly longer half-lives and have very large therapeutic indices. Since developing compounds that possess a quantum jump in the magnitude of either of the properties is likely to be difficult and time consuming, it would seem appropriate to seek novel means of delivering the existing drugs. The objective of this project was to prepare a biodegradable delivery system of buprenorphine that can be implanted subcutaneously and will release the drug for approximately 1 month at relatively constant rates sufficient to treat addiction.

MATERIALS AND METHODS

Materials

The copolymer poly(DL-lactic/glycolic acid) (PLGA 50/50; Resomer RG 506; inherent viscosity 0.8 dl/g) was obtained from Boehringer Ingelheim, Germany. The surfactant L-α-phosphatidylcholine was obtained from Avanti Polar-lipids, Incorporated (Albaster, AL). Buprenorphine, polyvinyl alcohol (PVA), chloroform, and dichloromethane were obtained from Sigma Chemical Company (St. Louis, MO).

Experimental Methods

Preparation of Biodegradable Microcapsules

Controlled-release biodegradable microcapsules of buprenorphine were prepared using PLGA (50/50) using procedures based on an in-water drying process in a complex emulsion system. These procedures differ in the way the organic solvent was eliminated: (*a*) evaporation (25) or (*b*) extraction (26). A specific amount (as listed in Table 1) of buprenorphine powder was dissolved in 500 μl

Table 1

Batch Formulas of Buprenorphine Microcapsules

Batch	Drug Loading (%)	Solvent Elimination Method	Aqueous Phase 0.3% PVA Plus
A	5	Evaporation	—
B	10	Evaporation	—
C	20	Evaporation	—
D	5	Evaporation	0.01% buprenorphine
E	5	Evaporation	0.05% buprenorphine
F	5	Extraction	Followed by isopropanol (2%)

of deionized water and then emulsified in 2 ml of dichloromethane containing 200 mg of PLGA. The PLGA solution was previously mixed with 200 µl of lipophilic surfactant L-α-phosphatidylcholine in chloroform (8 mg/ml). The emulsification was carried out by sonication at output 4 (50 W) for 30 sec (ultrasonic probe, Sonic and Materials, Inc., Danbury, CT). The resulting emulsion was further emulsified in 2 ml of an aqueous solution of PVA (1%) by vortexing for 15 sec and then was diluted in 100 ml PVA aqueous solution (0.3%). The system was stirred magnetically for 5 hr to allow complete evaporation of the solvent during the solvent elimination by evaporation. During the solvent elimination by extraction, the system was stirred for 10 min and then poured into 200 ml of an aqueous solution of isopropanol (2%) to extract dichloromethane to the external aqueous phase, and the stirring continued for an additional 2 hr.

Buprenorphine microcapsules were finally collected by centrifugation at 3000 rpm and washed four times with deionized water to remove any residual PVA on the surface of the microcapsules. The microcapsules were later freeze-dried to obtain a free-flowing powder.

Determination of Total Content

For each formulation, a 20-mg sample was dissolved in 1 ml of dichloromethane. To the solution, 4 ml of methanol was added, followed by ultracentrifugation (35,000 rpm at 15°C) to separate the precipitated copolymer completely. The amount of buprenorphine was determined by measuring the absorbance of clear supernatant in a spectrophotometer (DU 640, Beckman, Fullerton, CA) at 210 nm. Each experiment was performed in triplicate.

In Vitro Dissolution Studies

For each formulation, a 20-mg sample was placed in a 10-ml tube and incubated in 6 ml of deionized water with constant shaking (20 rpm) at 37°C. Samples (600 µl) were collected at scheduled times using a filter pipette and centrifuged for 10 min at 10,000 rpm. The sample was spectrophotometrically analyzed for buprenorphine content. Fresh deionized water was added to the incubated sample (600 µl) to maintain sink conditions. Dissolution studies were performed independently in triplicate.

Particle Size and Morphology

Size, morphology, and surface appearance of microcapsules were examined by scanning electron microscopy (SEM) (Amray AMR 1000A, Bedford, MA). Samples for SEM were mounted on metal stubs and coated with gold to a thickness of 200–500 Å. Pictures were taken, and the microcapsule sizes were determined according to a reference scale.

Statistical Analysis

The efficiency of encapsulation of buprenorphine and the amount of drug released form the different formulations of microcapsules during the in vitro study were compared using the SAS software package. A p value of less than 0.5 was considered as evidence of a significant difference.

RESULTS AND DISCUSSION

Several formulation and processing factors of the manufacturing process were changed to evaluate their effect on the resulting microcapsules: drug loading, partial saturation of the aqueous phase during the in-water solvent evaporation, and the solvent elimination procedure. Three batches of microcapsules (batches A–C) were prepared to study the effect of drug loading. Two batches of microcapsules (batches D, E) were prepared to study

the effect of partial saturation of the aqueous phase with buprenorphine during the in-water solvent evaporation. The effect of the solvent elimination procedure was studied by preparing another batch of microcapsules (batch F) in which the organic solvent was finally eliminated through extraction, unlike the first five batches, in which the solvent was eliminated through evaporation. The results obtained from the evaluation of these batches are listed in Table 2.

Efficiency of Encapsulation

The efficiency of encapsulation of buprenorphine was determined by measuring the amount of buprenorphine present in each 20-mg sample of the microcapsules (i.e., core loading experimental) and comparing this value with the expected amount of buprenorphine in each of the samples based on the drug loading during the preparation (i.e., core loading theoretical). As listed in Table 2, the maximum efficiency of encapsulation achieved was 37% (batch E). The efficiency of encapsulation increased from 11% to 34% when the drug loading was reduced from 20% to 5%.

The overall efficiency of encapsulation of buprenorphine in each of these batches was significantly less than expected. This poor encapsulation may be due to the diffusion of buprenorphine to the aqueous phase during the final in-water solvent evaporation. In an attempt to minimize the drug loss during the in-water solvent evaporation, the final aqueous phase was partially saturated with buprenorphine (0.01% and 0.05%). These two batches of the microcapsules (batches D and E) were compared with control microcapsules (batch A). Each of these batches was prepared with the same amount of buprenorphine. Moreover, all three batches experienced the same process up to the formation of the water/oil/water emulsion. During the in-water solvent evaporation, the aqueous phase containing 0.3% PVA was partially saturated with 0.01% and 0.05% buprenorphine for batches D and E. However, there was no significant difference ($p > .05$) in the efficiency of encapsulation among these three batches. Similar results were also observed when the solvent removal process was changed from in-water evaporation to evaporation followed by extraction in isopropanol (2%). No significant ($p > .05$) change in the efficiency of encapsulation was observed between batch A and batch F.

Dissolution of Buprenorphine

The dissolution of buprenorphine was compared by calculating the cumulative percentage of the drug released at a specific sampling time (Figs. 1 and 2). All five batches of the microcapsules were free from initial ''burst effect.'' Figure 1 shows the effect of drug loading on the in vitro dissolution characteristics of the microcapsules (batches A–C). These three batches of the microcapsules showed a statistically similar amount of drug release during the first 4 days. The drug release during the first 24 hours was between 2% and 3%. A difference in dissolution due to a difference in the drug loading was observed between 6 and 30 days. The microcapsules prepared with 5% loading showed minimum drug release during this period, followed by the microcapsules prepared with 10% and 20% loading, respectively. However, all three batches of the microcapsules showed a significantly high drug release between 30 and 45 days. The cumulative amount of drug release at the end of 45 days was between 63% and 64%.

Figure 2 shows the dissolution profiles of batches A and D–F. All four batches of the microcapsules showed no significant initial burst effect during the dissolution study. A comparison among batches A, D, and E shows

Table 2

Characteristics of Buprenorphine-Loaded PLGA Microcapsules

Batch	Average Particle Size (Range) (μm) ($n = 100$)	Efficiency of Encapsulation[a] (%), Mean (±SD) ($n = 3$)	Physical Appearance
A	20 (4–40)	34.42 (0.76)	Smooth, spherical
B	17 (4–36)	19.76 (0.87)	Smooth, spherical
C	14 (3–28)	11.19 (1.02)	Smooth, spherical
D	19 (4–42)	32.08 (1.64)	Smooth, spherical
E	17 (3–26)	36.79 (1.18)	Smooth, spherical
F	49 (20–84)	32.50 (1.23)	Slightly irregular, porous

[a] Efficiency of encapsulation = (core loading experimental)/(core loading theoretical) × 100.

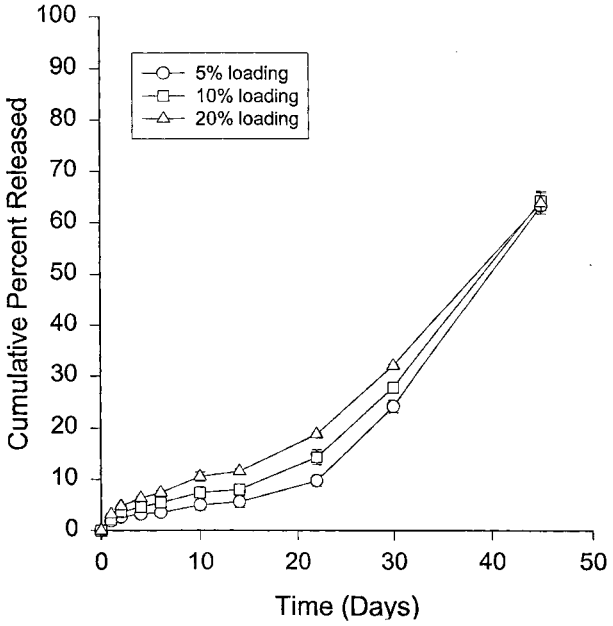

Figure 1. Dissolution profiles of buprenorphine microcapsules from batches A, B, and C.

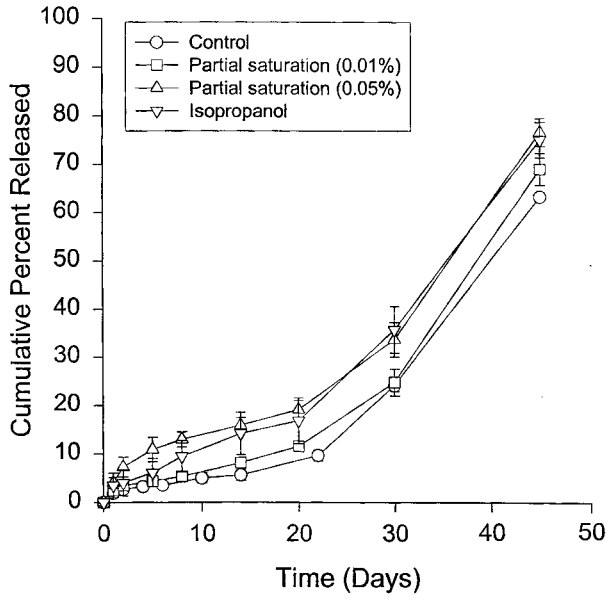

Figure 2. Dissolution profiles of buprenorphine microcapsules from batches A, D, E, and F.

the effect of partial saturation of the aqueous phase during the in-water solvent evaporation on the dissolution of buprenorphine. The cumulative amount of drug released within the first 24 hours was not significantly different from one another. However, a partial saturation of the aqueous phase with 0.05% buprenorphine (batch E) resulted in higher dissolution during the early stage of the dissolution study compared with batch A (control) and batch D (partial saturation with 0.01% buprenorphine). This trend continued throughout the dissolution study. The microcapsules prepared by solvent extraction (batch F) also showed increased dissolution. The cumulative amount of buprenorphine released from these microcapsules was identical to the release from batch E following the first 2 weeks of the dissolution study. Since all four batches of the microcapsules (batches A, D–F) contain a statistically similar amount of buprenorphine, this increased dissolution from the last two batches was mainly due to faster degradation of the matrix because of a change in the solvent removal process.

Particle Size and Morphology

A comparison of the particle size reveals a similar average particle size in the first four batches (A–E) of the microcapsules (Table 2). The particles were all less than 50 μm, with a range of average sizes from 14 μm to 20 μm in diameter. This observation shows that a change in the drug loading from 5% to 20% did not produce any significant difference in the microcapsule size. A similar conclusion was applicable to the microcapsules prepared by partial saturation of the aqueous phase. However, the microcapsules prepared by solvent extraction (batch F) resulted in a larger particle size (average diameter 49 μm) compared with the first four batches of the microcapsules. These microcapsules were all less than 90 μm.

The scanning electron micrographs of the microcapsules are presented in Fig. 3. The first four batches of the microcapsules were all smooth and spherical. However, the microcapsules of batch F were slightly irregular and porous. These observations showed that a change in drug loading, within the studied range, produced no significant morphological change. A similar conclusion was also true for batches D and E. A partial saturation of the aqueous phase with buprenorphine, within the studied range, did not change the surface morphology. However, the microcapsules prepared by the extraction were different from the other batches. These microcapsules were all slightly irregular and porous. This change in the morphology was due to the change in the solvent removal procedure. The morphology of these microcapsules had

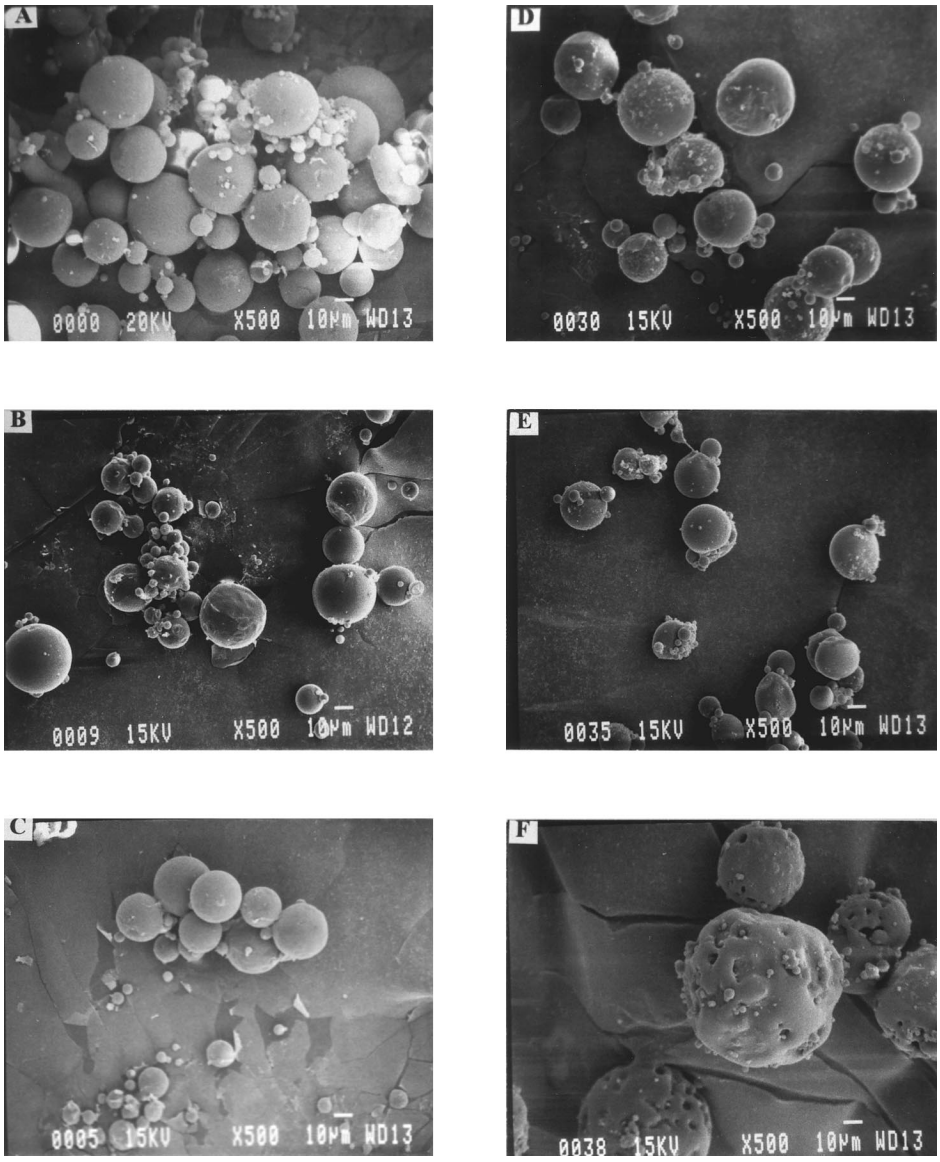

Figure 3. SEM photographs of buprenorphine microcapsules from batches A–F.

changed due to a change in PLGA precipitation characteristics. During the extraction of dichloromethane in isopropanol solution, the polymer precipitated at a faster rate, which resulted in a porous microcapsule.

CONCLUSIONS

The overall results presented in this study provide evidence that the efficiency of encapsulation of buprenorphine increases with the decrease of the drug loading. This increase in the efficiency of encapsulation may be due to a decrease in the amount of buprenorphine diffused to the external aqueous phase during the in-water solvent evaporation. However, no significant change in the efficiency of encapsulation was obsserved by partial saturation of the aqueous phase with buprenorphine or by changing the solvent removal process from evaporation to extraction into 2% isopropanol. A change in the solvent removal process from evaporation to extraction

increased the overall dissolution of the microcapsules. The solvent extraction procedure also resulted in porous microcapsules. The average particle size of the microcapsules prepared by solvent extraction was relatively larger than the other batches. However, the size of the microcapsules in all the batches prepared for this study is less than 100 μm, and thus they are suitable for subcutaneous or intramuscular administration using a 20-gauge needle.

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