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Long-Acting injectable buprenorphine PLGA microparticle formulation☆

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ABSTRACT

Opioid use disorder (OUD) continues to be a major cause of morbidity and mortality globally. Medications for opioid use disorder have shown promise in reducing the illicit use of opioids, resulting in reduced overdose deaths and healthcare costs. Buprenorphine is a widely used drug for treating OUD with attributes favorable for long-acting formulations. The goal of this study was to develop a 3-month long-acting injectable buprenorphine microparticle formulation for treating OUD. The target product profile of the buprenorphine formulation consisted of a loading of 35–40 % and *in vivo* drug release for ≥3 months. To achieve this goal, we utilized a solid-in-oil-in-water (S/O/W) emulsion technique and defined the critical material attributes of PLGA (85:15, MW = 108 kDa) at 15.2 % w/v in oil phase and critical processing parameters including the use of ethyl acetate as the oil phase solvent and post-particle formation treatment using a 25 % ethanolic solution for 8 h. A pharmacokinetic (PK) study in the rat model shows that the buprenorphine concentration was ≥ 2 ng/mL for over 60 days and then ≥ 1 ng/mL for another 40 days, maintaining the buprenorphine concentration above 1 ng/mL; equivalent to the levels observed in other commercially available formulations for a longer-release time. Our study has shown the feasibility of making long-acting PLGA microparticles for buprenorphine release for ≥3 months using the S/O/W emulsion method.

1. Introduction

1.1. Opioid use disorder and buprenorphine

Opioid use disorder (OUD) has become an epidemic in the United States, and accessible OUD treatments are urgently required (Rosenthal, 2019). OUD is a chronic relapsing disorder, but successful recovery is possible with appropriate treatment (Strang et al., 2020). However, it comes with a persistent propensity to relapse. Clinical trials demonstrated that long-term opioid agonist therapy was effective for OUD treatment (Strang et al., 2020). Untreated OUD, a chronic brain disease, has a serious cost to people, their families, and society. For example, each year, opioid overdose, misuse, and dependence account for $35 billion in health care costs, $14.4 billion in criminal justice costs, and $92 billion in lost productivity (PEW, 2021). Around 114,000 drug overdose deaths occurred in 2023, and the number decreased to about 87,000 in 2024 (CDC, 2025). Such a dramatic decrease in overdose deaths is partly due to the widespread, data-driven contribution of naloxone, which can quickly reverse an overdose, and better access to evidence-based treatment for substance use disorders (CDC, 2025). Still, the number of deaths is unacceptably high.

Medication for opioid use disorder has been shown to increase treatment retention for OUD (Mattick et al., 2014), a reduction in illicit opioid use (Knittel et al., 2023), an improvement in neonatal outcomes for babies born to women with OUDs (Knittel et al., 2023), a reduction in opioid-related mortality rates (Sordo et al., 2017), and a reduction in substantiated cases of child abuse and neglect (Morris et al., 2019). Mortality related to OUD has been reduced by opioid agonist therapy (OAT), including buprenorphine and methadone (Barnett et al., 2021). Methadone is a synthetic, full agonist of the μ-, κ-, and δ-opioid receptors, causing a higher risk for respiratory depression and higher comorbid mental disorders than buprenorphine (Leshner and Mancher, 2019; Soyka, 2021). On the other hand, buprenorphine is an opioid partial agonist of the μ-opioid receptors and an antagonist to the κ −opioid receptor, producing effects such as euphoria or respiratory depression at low to moderate doses, which are weaker than methadone and heroin (SAMHSA, 2022). Thus, buprenorphine has been used widely to treat OUD as a medication-assisted treatment (MAT). MAT is the use

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of medications in combination with counseling and behavioral therapies (FDA, 2022). Since buprenorphine is prescribed or dispensed in physician offices, it significantly increases access to treatment (SAMHSA, 2022). Quality of life is a crucial construct in assessing outcomes of substance use treatment interventions. Buprenorphine treatment is known to improve the overall physical, psychological, and social quality of life for individuals with OUD (Blumberg et al., 2017; Golan et al., 2022).

1.2. Current buprenorphine formulations available to patients

Buprenorphine has been in clinical use for over 25 years. The buprenorphine products approved by the FDA for the treatment of OUD include buprenorphine sublingual tablets (Subutex®), buprenorphine/naloxone sublingual films (Suboxone®), rapidly dissolving buprenorphine/naloxone sublingual tablet (Zubsolv®), and buprenorphine/naloxone buccal film (Bunavail®). The oral formulations have considerable diversion of the medications and risks of nonadherence. In addition to oral formulations, prolonged-release buprenorphine formulations have been developed, improving patients' convenience and compliance. One such product was 6-month Probuphine® (Chappuy et al., 2021), a six-month-long implant requiring surgical placement and removal (2016), and withdrawn from the market in 2018 (Clemans-Cope et al., 2020). Currently, there are two injection depots: 1-month Sublocade® (a biodegradable polymer formulation) and once-a-week or once-a-month Brixadi® (a liquid crystal formulation).

A comparison study showed that using Probuphine implants resulted in higher treatment retention rates and reduced illicit opioid use than oral formulations (Harricharan and Farah, 2017; Larance et al., 2014; Ling et al., 2019; Mitchell et al., 2021; Mumenthaler and Beebe, 2015). The benefits of long-acting injectable formulations over take-home medications have been recognized for decades, and various formulation approaches have been made (O'Brien et al., 2021). Long-acting injectable formulations tend to avoid daily fluctuations in plasma concentrations, abuse, diversion, and risk of non-medical use (Barnett et al., 2021; Larance et al., 2014; Stein et al., 2022). Another critical benefit of long-acting formulations is that the increased compliance with medication avoids lapses in medication intake for a few days that may occur with oral, daily formulations. It prevents returning to illicit opioid use (Stein et al., 2022).

1.3. PLGA-based long-acting injectable (LAI) formulations

Since the introduction of Lupron Depot®, the first long-acting injectable microparticle formulation approved by the U.S. Food and Drug Administration (FDA) in 1989, only 27 long-acting formulations have been approved during the last 36 years (Park, 2025). Such a low number of approved long-acting products highlights the difficulty of making long-acting injectable depot formulations. Currently, all long-acting injectable formulations are based on biodegradable poly (lactide-co-glycolide) (PLGA) polymers. PLGA naturally degrades in the body, and the degradation kinetics depend on the L:G ratio. To date, most PLGA formulations have been developed by trial and error. The limitations of this approach include the absence of guiding scientific principles for the rationale design of target formulations, and the inability to know the precise causes of success or failure for further improvements.

The PLGA-based injectable formulations require no surgical implantation and removal, thereby eliminating any side effects associated with the surgery necessary for implants. The current injectable formulations deliver buprenorphine only for up to a month. Sublocade® is an *in situ* forming implant (ISFI) composed of buprenorphine and PLGA 50:50 with a carboxylic acid end-group (i.e., lactide:glycolide = 50%:50%) dissolved in N-methyl-2-pyrrolidone (NMP), delivering 100 mg (in 0.5 mL solution) or 300 mg (in 1.5 mL) of buprenorphine over a month (Indivior, 2018). Upon subcutaneous injection, the solvent NMP is removed by absorbing into the body, causing the PLGA to become a solid-like formulation that can release buprenorphine for a month. This ISFI approach of using NMP is known as the Atrigel® technology (Dunn et al., 1990; Dunn et al., 1997). For PLGA 50:50, it generally takes about a month to degrade, but molecular weight and end-group can influence the degradation rate. The 300 mg formulation is used for the first two months, followed by a monthly maintenance dose of 100 mg. The controlled trials indicated that using a 300 mg maintenance dose is not superior to using a 100 mg dose (Chappuy et al., 2021). It provides buprenorphine plasma levels of $\geq$ 2 ng/mL for clinically meaningful withdrawal suppression and opioid blockade (Laffont et al., 2016).

It is necessary to develop a new long-acting injectable (LAI) PLGA formulation delivering buprenorphine for much longer than a month for patients' convenience and compliance. Of the three PLGA-based formulations, microparticle formulations appear to be ideal considering the $\geq$3 months delivery and the required dose. Microparticles can be made by various methods, including oil/water (O/W) emulsification, membrane emulsification, microfluidics, spray drying, and coaxial electrospraying. In terms of the yield, speed of manufacturing, and cost, O/W emulsification is most efficient, reliable, and superior to other methods (Lee et al., 2019).

The aim of this study is to demonstrate a viable methodology to formulate and manufacture a high drug loaded buprenorphine PLGA microparticle formulation for 3-month delivery.

2. Materials and methods

2.1. Materials

Buprenorphine HCl and free base were obtained from SpecGx, LLC (St. Louis, MO). PLGA was obtained from Corbion N.V. (Amsterdam, Netherlands). Ethyl acetate (EA), ethyl formate (EF), acetonitrile, ethanol, potassium phosphate monobasic, sodium dodecyl sulfate, and sodium azide were procured from Fisher Scientific (Fair Lawn, NJ). Emprove® Essential 40–88 (poly(vinyl alcohol) (PVA)) was obtained from Millipore Sigma (Darmstadt, Germany). Phosphate-buffered saline with 0.05 % Tween® 20, pH 7.4 (PBST) was purchased from Sigma Aldrich (St. Louis, MO).

2.2. Buprenorphine PLGA microparticles by S/O/W emulsion method

Fig. 1 shows the chemical structure of the buprenorphine base form. A solid-in-oil-in-water (S/O/W) emulsification technique was used to prepare long-term ($\geq$3 months) injectable buprenorphine microparticle formulations. The poor solubility of buprenorphine in organic solvents and hydrophobicity of buprenorphine free base provided an opportunity to formulate into microparticles via a S/O/W emulsion approach, as shown in Fig. 2. The processing and formulation variables that could

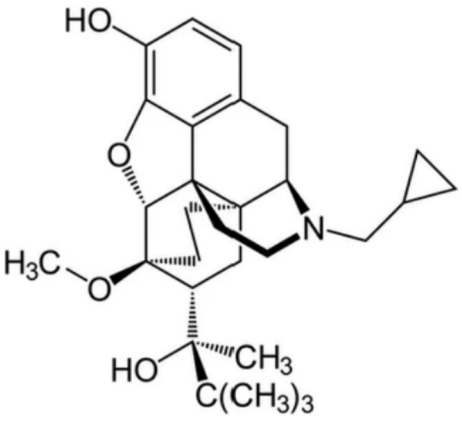


Fig. 1. Buprenorphine chemical structure.

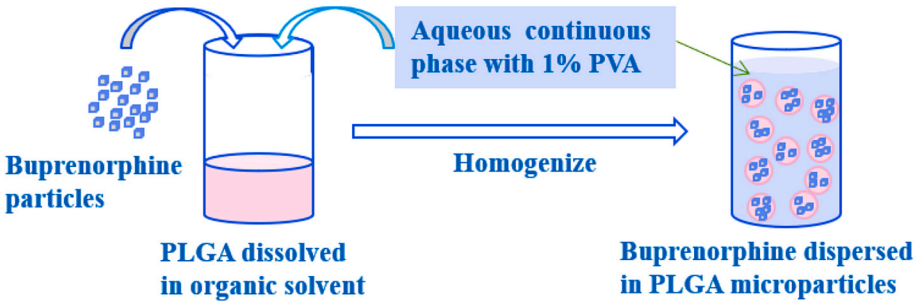


Fig. 2. An S/O/W emulsion method was used to prepare buprenorphine-loaded PLGA microparticles dispersed in a continuous aqueous phase. The prepared PLGA microparticles were subsequently treated with a 25% ethanol solution.

impact the prepared microparticle properties are listed in Table 1. In addition, we examined the impact of buprenorphine particle size because of our S/O/W emulsion method.

Buprenorphine particles were sieved through a specific size to remove oversized particles, a 63 or 53 μm sieve as noted in Table 1. PLGA (Purasorb® from Corbion) was dissolved in ethyl formate (**EF**) or ethyl acetate (**EA**) at 22 °C in a 20 mL scintillation vial. Buprenorphine was then loaded into said scintillation vial with the PLGA solution and mixed on a vortex mixer for ~ 15 min. This suspension was then homogenized at 6,000 RPM for 60 sec with an IKA T25 homogenizer with an S25N-10G generator. 7.5 mL of continuous phase (1 % PVA) was added to the vial via a pipette and was homogenized at 4,500 RPM for 60 sec. This seed emulsion was immediately transferred to an aqueous extraction phase at 4 °C for 16 hr. Both continuous and extraction phases were added with either EF or EA to slow the solvent extraction rate into water, leading to slow the precipitation of PLGA and a more compact microparticle structure. The microparticles were collected between a 25 and 150 μm sieve and vacuum dried. An additional post-treatment was done in a 25 % ethanol solution for 2–8 h.

2.3. X-ray powder diffraction

X-ray powder diffraction (XRD) was used to identify the percent crystallinity of buprenorphine and the respective crystalline forms if others than the free base exist). The data was collected on a Panalytical Empyrean X-ray diffractometer equipped with Bragg-Brentano HD optics, a sealed tube copper X-ray source (λ = 1.54178 Å), soller slits on both the incident and receiving optics sides, and a PixCel3D Medipix detector. Samples were packed in metal sample cups with 16 mm wide and 2 mm deep sample areas. Anti-scatter slits, divergence slits, and masks were chosen based on sample area and starting θ angle. Data was collected between 4 and 30° in 2θ using the Panalytical Data Collector software.

To date, only the free base form and HCl salt form of buprenorphine have been disclosed in the Cambridge Structural Database, identifiers BOCYAV, and SUNWAZ.

2.4. High-performance liquid chromatography (HPLC)

Buprenorphine quantitation was performed with an Agilent 1260 HPLC system with a UV absorbance detector. The HPLC had the following conditions: Mobile Phase: 83:17 acetonitrile:potassium phosphate buffer (10 mmol), pH 6.0; flow rate: 1.0 mL/min; autosampler temperature: room temperature; column temperature: 30 °C; detection: 210 nm (UV); total run time: 10 min; injection volume: 2.5 μL (drug loading) 20 μL (*in vitro* release); column: Zorbax SB-C18 150 × 4.6 mm, 5 μm; and approximate retention time of buprenorphine: 7.6 min.

2.5. Buprenorphine drug loading

Approximately 3–5 mg of the buprenorphine microparticles were weighed, dissolved in 5 mL of acetonitrile + 1 mL of dimethylacetamide, and subsequently diluted with the mobile phase. 2.5 μL was then injected with the same HPLC conditions as the *in vitro* release samples.

2.6. In vitro release study

Currently, there are no compendial or biorelevant *in vitro* dissolution tests, i.e., drug release tests, for long-acting injectable depot formulations, such as microparticles. Our preliminary study examined USP 4 and orbital agitation methods for drug release from PLGA microparticles and found that the orbital agitation method is more straightforward and reproducible. Thus, long-term buprenorphine release was studied using the shake-flask orbital rotation method at 37.0 °C (Garner et al., 2018). Erlenmeyer flasks with rubber stoppers containing ~ 3–5 mg of buprenorphine microparticles were used to test multiple formulations simultaneously. Due to the extremely low solubility of buprenorphine FB, *in vitro* release testing was done in 50 mL of 0.5 % sodium dodecyl sulfate (0.5 % SDS) or PBS with 0.05 % Tween 20 (PBST) at 37 °C (Otte et al., 2021). Release samples (1 mL 0.5 % SDS and 10 mL PBST) were taken frequently to try and maintain sink conditions and replaced with fresh release media. These studies were performed under sink conditions and representative buprenorphine concentrations in the release media were determined via HPLC.

2.7. Imaging

The morphology of buprenorphine microparticles was characterized with a Tescan Vega 3 scanning electron microscope. Microparticles were mounted onto double-sided carbon taped aluminum stubs and sputter-coated with a gold–palladium mixture under vacuum in the presence of argon.

2.8. Particle size analysis

The particle size distribution was measured using a CILAS 1190 particle size analyzer (CPS US, Inc). Approximately 50 mg of microspheres were dispersed in 1.5 mL of a 0.1 % Tween 80 aqueous solution and subsequently analyzed.

2.9. Thermal analysis

A Perkin Elmer DSC 7 was used for thermal analysis. Samples (~3–5 mg) were analyzed in aluminum pans under a dry nitrogen purge at 20 mL/min. Indium was used for temperature and heat of fusion calibration (ΔH_f). Samples were heated at 20 °C/min to temperatures approximately 40 °C above the glass transition (T_g).

2.10. In vivo pharmacokinetics in the rodent model

Sprague-Dawley male rats weighing 300–350 g (n = 3 rats/formulation) were injected into the subcutaneous space of the back at an

Table 1
Buprenorphine-loaded PLGA microparticle batches prepared under different processing conditions.

Batch #	Buprenorphine Form (size)	Target Drug Loading (%)	Actual Drug Loading (%)	Processing Notes
PLGA microparticles prepared with ethyl formate (EF)				
1	**HCl Salt**	**35**	16.1	PLGA: 85:15-Ester(E),
2	**(<63 μm)**	**45**	16.5	**0.74 dL/g** (M_w = 89
3	**Free base (FB)**	**35**	32.4	kDa),
4	**(<63 μm)**	**40**	41.1	PLGA 16.6 % w/w in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP)
5	FB (<53 μm)	40	35.4	PLGA: 85:15-E, **0.87 dL/g** (M_w = 108 kDa), PLGA 16.6 % w/w in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP)
6	FB (<53 μm)	40	34.3	PLGA: 85:15-E, **0.95 dL/g** (M_w = 128 kDa), PLGA 16.6 % w/w in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP)
7	FB (<53 μm)	40	28.7	PLGA: 85:15-E, **0.87 dL/g** (M_w = 108 kDa), PLGA 16.6 % w/w in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP) **8 hr 25 % EtOH wash**
8	FB (<53 μm)	40	28.8	PLGA: 85:15-Ester, **0.95 dL/g** (M_w = 128 kDa), PLGA 16.6 % w/w in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP) **8 hr 25 % EtOH wash**
9	FB (<53 μm)	40	29.1	PLGA 85:15-E, **0.87 dL/g** (M_w = 108 kDa) PLGA 16.6 % w/w dissolved in EF, 6 % EF in 1 % PVA H_2O (CP), 2.5 % EF in H_2O (EP)	**2 hr 25 % EtOH Wash**
10	FB (<53 μm)	40	27.4		**4 hr 25 % EtOH Wash**
11	FB (<53 μm)	40	28.3		**6 hr 25 % EtOH Wash**
12	FB (<53 μm)	40	27.3		**8 hr 25 % EtOH Wash (Repeat #7)**
PLGA microparticles prepared with ethyl acetate (EA)				
13	FB (<53 μm)	40	33.6	PLGA: 85:15-E, **0.87 dL/g** (M_w = 108 kDa) 6 % EA in 1 % PVA H_2O (CP), 2.5 % EA in H_2O (EP), 8 hr. 25 % EtOH Wash	**PLGA in EA at 23.1 %**
14	FB (<53 μm)	40	38.2		**PLGA in EA at 18.4 %**
15	FB (<53 μm)	40	40.7		**PLGA in EA at 15.2 %**
16	FB (<53 μm)	40	41.3		**PLGA in EA at 13.0 %**

Animal Equivalent Dose (AED) of 31 mg/kg, where AED = Human dose (mg/kg) × K_m ratio, with 300 mg of buprenorphine over 3 months (100 mg/month), 60 kg for human weight, and a $K_m$ratio of 6.2. Rats were anesthetized with isoflurane (4–5 % induction, 1–2 % maintenance, ~500 mL/min O_2), and the buprenorphine microparticles were injected into the dorsal scapular region with a 20G needle. Prior to injection, the microparticles were suspended in 1 mL of diluent composed of 0.9 % w/w sodium chloride, 0.02 % w/w polysorbate 20, 0.5 % w/w carboxymethylcellulose sodium salt (CMC), and water for injection. The animals were observed for overt toxicity and any existing test site abnormalities during the study, including redness, swelling, bleeding, discharge, and bruising at the insertion site. Body weights were taken at each blood draw. Blood samples were collected from the tail vein (250 μL) of the rat at 2, 6, 24, and 48 h and 3, 5, 7, 10, 14, 17, 21, 28, and every 7 days thereafter until day 105, treated with an anticoagulant (K_2EDTA), cold centrifuged (10,000 RPM, 10 min, 4 °C) to separate plasma, and stored (−80 °C) prior to analysis. Analysis was done with liquid chromatography-tandem mass spectrometry/mass spectrometry (LC-MS/MS) at Inotiv in Fort Collins, CO. LC-MS/MS methods for buprenorphine from plasma (Harricharan and Farah, 2017; Larance et al., 2014; Mumenthaler and Beebe, 2015) was used as is or slightly modified for optimization on the instrument used. The animal study was approved by the Purdue Institutional Animal Care and Use Committee in conformity with the NIH guidelines for the care and use of laboratory animals.

3. Results

3.1. Buprenorphine microparticle formulations

Long-acting injectable buprenorphine microparticle formulations were developed based on the Quality by Design (QbD) approach. First, the quality target product profile (QTPP) was constructed, which is to maintain the buprenorphine plasma concentration at ≥ 0.7 ng/mL for ≥ 3 months and a burst release less than or equal to Probuphine formulation (< 3 ng/mL). Both QTPP and CQAs are affected by a large number of variables in the critical material attributes (CMAs) and critical process parameters (CPPs) (Park et al., 2021a, b). For the potential CMAs, the microparticle compositions, such as buprenorphine form, PLGA type, and PLGA concentration, were examined. Potential CPPs were examined using various manufacturing processes, including continuous phases, solvent extraction phases, and ethanol (EtOH) post-treatment. Table 1 shows the buprenorphine microparticle batches prepared under different MAs and PPs. It illustrates the respective drug loadings of the microparticle batches prepared and some highlights of the processing conditions as formulation feasibility moves closer to the target of 3 months of release.

Selection of buprenorphine form: The initial experiments used the buprenorphine HCl salt form and compared it with a buprenorphine-free base (FB) (**Batches 1–4 in** Table 1**)**. Microparticles prepared using buprenorphine-HCl suffered from low drug loading. Thus, the subsequent experiments focused on using the buprenorphine-FB (**Batches 3–16**) and altering the organic phase viscosity, modifying continuous and extraction phases, and adjusting post-treatment process.

The buprenorphine FB crystals were passed through a 53 μm sieve prior to encapsulation into the microparticles. It's highly probable that the PLGA particles < 25 μm contain low levels of buprenorphine based on the buprenorphine crystal size distribution. As microparticles were collected on top of a 25 μm sieve, it appeared to result in a 'loss' of PLGA, resulting in a more significant percentage of buprenorphine recovered.

Selection of PLGA: PLGAs with higher L:G ratios and molecular weights allow higher drug loading, prolonged drug release, and reduced initial burst release (Kamali et al., 2019; Koocheki et al., 2011; Richey and Thanoo, 2016; Tice et al., 2002; Yoon et al., 2021). Based on our experiences in making PLGA microparticles for 1 ~ 6 months of delivery, we used PLGA 85:15 polymers with ester endcap (from Corbion with the IV ranging from 0.74 to 0.95 dL/g).

Selection of organic solvents: The solvent's water-solubility affects the properties of the final PLGA microparticles, e.g., microstructural density, drug distribution, and interconnected pores, that contribute to the initial burst release (Park et al., 2021a, b). For PLGA 85:15, most

organic solvents can be used to dissolve the polymers (Garner et al., 2021; Skidmore et al., 2019). Of the solvent, poorly water-soluble solvents are preferred for forming densely packed PLGA microparticles (Park et al., 2021a; Park et al., 2019). For example, benzyl alcohol has a water solubility of 3.5 %. Although it is difficult to remove due to its high boiling point of 205 °C, and the remaining solvent in microparticles affects drug release kinetics and long-term stability of the formulation. The water solubilities of EF and EA are 10.5 % and 8.0 %, respectively (Yeo et al., 2003). While these water solubility values are relatively high, buprenorphine is poorly soluble in both. For these reasons, we compared EF (for **Batches 1–12**) and EA (for **Batches 13–16**).

3.2. Buprenorphine loading and microparticle size

As shown by **Batches 3–12** using ethyl formate in Table 1, the actual loading without post-EtOH treatment (32.4 ~ 41.1 % in **Batches 3–6**) was higher than with post-EtOH treatment (27.3 ~ 29.1 % in **Batches 7–12**). The post-EtOH treatment lowered the drug loading, but it significantly affected the drug release kinetics (see below). Microparticles of **Batches 7–8** were imaged by SEM (Fig. 3). The figure highlights the images of Batch 8, showing discrete crystals of buprenorphine-FB (arrows in C and D). The free base form of buprenorphine may be responsible for sustained release in aqueous solution due to its poor water solubility.

All the batches of microparticles exhibit an extremely rugged spherical shape, likely due to the buprenorphine crystals dispersed throughout individual microparticles (Fig. 3). No observable differences were found between **Batches 9–12**, indicating that ethanol wash duration does not alter the particle or surface morphology. The impact of the starting concentration oil dispersion solution in **Batches 13–16** is readily apparent in observable differences in the microparticle surfaces as shown in Fig. 4. A significant amount of surface porosity is noted for **Batch 13**, the highest PLGA concentration of this study, with the surface porosity appearing to decrease as a function of starting concentration. This surface porosity also correlates with the drug release and loading, as **Batch 13** showed the largest initial release rate coupled with the lowest drug loading (see below).

Batches 13–16 were performed as initial tests to understand the impact of using ethyl acetate as a solvent system coupled with the starting oil phase viscosity, as previous studies used ethyl formate. As the viscosity of the solution decreased over Batch 13 through Batch 16, the encapsulation efficiency increased. The larger than 100 % encapsulation efficiency for Batch 16 is likely a result of fine (<25 μm) PLGA particles that are lost during sieving, as these may be predominately polymer.

Particle size distributions of buprenorphine and the prepared microparticle batches were analyzed with the respective d_{10}, d_{50}, and d_{90} shown in Table 2. As described in the manufacturing, microparticles were collected on a 25 μm sieve with a scalping sieve of 150 μm used to remove any oversized particles. This is a commonly used size range for long-acting injectable products and used to normalize the particle size distribution across the various batches. A few batches have d_{90} values greater than 150 μm and this is likely due to the anisotropy of the microparticles, where microparticles with equivalent spherical diameters greater than 150 μm may traverse the sieves based upon an aspect ratio greater than one. There is a general trend with respect to viscosity and particle size distribution, where the higher the %w/w polymer concentration results in a slightly higher particle size values as illustrated in **Batches 13–16**.

3.3. Powder X-ray diffraction pattern (PXRD)

PXRD of **Batches 9–16** are shown in Fig. 5. The buprenorphine free base PXRD pattern is illustrated in Fig. 5**A**, as a reference. No observable differences are noted in the patterns for the batches shown, demonstrating that there does not appear to be any polymorphic or solvated forms generated during the manufacturing based upon the absence of any new diffraction peaks. This is advantageous as the processing does not appear to induce any issues with stability.

Thermal analysis was performed on **Batches 5–16** to determine the impact of the processing on the glass transition (T_g) (Fig. 5**D**). Aside from **Batches 9 and 10**, incorporation of buprenorphine nor the processing appears to influence the glass transition. **Batches 9 and 10** appear to be outliers unless there is a specific phenomenon ongoing. **Batches 5 and 6** are non-25 % EtOH-washed samples, with **Batches 7 and 8** washed for 8 hrs, although no difference in the T_g is observed. **Batches 9–12** are increasing 25 % EtOH time from 2 to 8 hrs, where similar T_g's are observed for the 2 and 4 hr wash time and the 6 and 8 hr. Future studies will be performed to determine if there is a specific plasticization effect as a function of ethanol wash time.

3.4. In vitro buprenorphine release study

Fig. 6 shows the *in vitro* release profiles. **Batches 1 and 2** (B1 and B2 in Fig. 6A) released all buprenorphine-HCl in 15 days due to its higher water solubility. The same processing parameters were then performed with the free base form, where a higher initial release rate was observed for the FB form. Although this is likely due to the differences in drug loading. The encapsulation efficiency (EE) of the HCl form was only 46 % and 37 % for B1 and B2, respectively. Therefore, future studies should focus on incorporating the FB form as the EE was 92 % and 103 % for B3 and B4, respectively. An EE greater than 100 % implies that PLGA is likely lost during the manufacturing. Higher MW PLGAs were used with B5 and B6 to potentially slow the initial release (Fig. 6B). A 25 % EtOH was incorporated into B7 and B8. The hypothesis was that the 25 % EtOH wash would age the microparticles, resulting in a reduction of free volume (porosity), thereby slowing the release rate. While the release rate is clearly reduced in the 25 % EtOH samples, this comes at the expense of a reduction in drug loading. The reduction in release rate may be attributed to a decrease in drug load or a combination of the two. The EE of B7 and B8 is ~ 72 %. This may be a satisfactory EE from a development standpoint, but there is significant room for improvement.

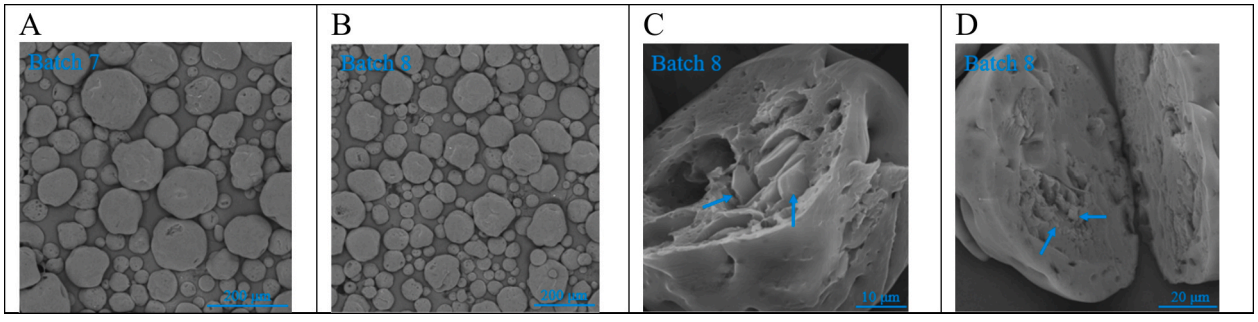


Fig. 3. SEM images of Batches 7 and 8 microparticles.

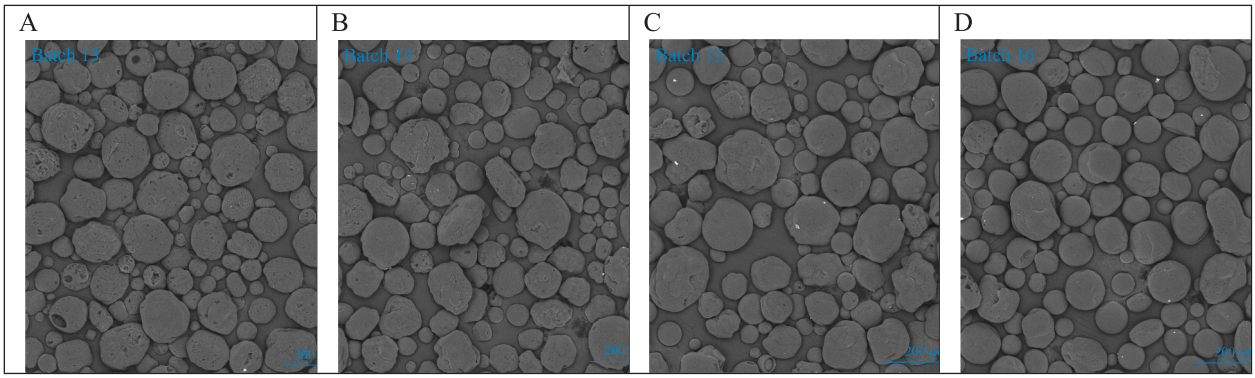


Fig. 4. SEM images of Batches 13–16 (A-D).

Table 2
d_{10}, d_{50}, and d_{90} of the particle size distribution of the buprenorphine-loaded PLGA microparticle batches.

	d_{10} [μm]	d_{50} [μm]	d_{90} [μm]
HCl Salt (<63 μm)	12.8	32.4	49.9
FB (<63 μm)	8.7	27.8	53.0
FB (<53 μm)	4.6	17.3	37.1
B1	47.7	86.8	138.6
B2	46.6	88.0	138.1
B3	39.4	64.2	100.7
B4	31.2	69.8	115.7
B5	57.2	101.8	152.2
B6	58.8	103.5	154.4
B7	49.5	90.8	142.1
B8	48.7	94.4	147.6
B9	56.4	91.4	137.2
B10	46.0	83.6	131.9
B11	55.1	89.6	131.5
B12	44.3	75.1	115.4
B13	55.6	104.2	162.8
B14	51.3	99.9	153.3
B15	49.8	89.3	139.9
B16	55.8	91.6	141.0

As minimal performance differences were noted between the 0.87 and 0.95 dL/g IV PLGA polymers, a study on the impact of 25 % EtOH wash time in the 0.87 dL/g was performed to balance potential drug loss with the *in vitro* release rate. An EtOH wash duration of either 2, 4, 6, or 8 hrs was performed on batches 9–12. The similar release profiles observed for Batches 9–12 (Fig. 6**C**) may be due to 2 factors: (i) the use of PLGAs of the same molecular weight regardless of the post-EtOH treatment time ranging from 2 hr to 8 hr, and (ii) the buprenorphine loading in these batches was similar, with EE of ~ 70 %. While the release profiles show a sustained release of greater than 3 mos, an increase in EE is still desirable. Experiments to date have used ethyl formate, whereas ethyl acetate was used for **Batches 13–16**. These two solvents were chosen based upon the poor solubility of buprenorphine in both, the PLGAs' respective solubility in both, and the poor solubility in water. Microparticles of **Batches 13–16** (prepared using ethyl acetate) demonstrate significantly different loading and release properties than those prepared using ethyl formate (Fig. 6**D**). This may be due to the use of different concentrations of PLGAs: as the PLGA concentration in ethyl acetate decreased from 23.1 % to 13.0 %, the drug release rate also decreased.

0.5 % SDS was chosen as a release medium based upon Kleppner et al. (Kleppner et al., 2006). PBST exhibits poor solubility for buprenorphine (i.e., difficulty in maintaining a sink condition) (*in vitro* release curves available in Supplementary Materials), and SDS may be too aggressive (which may be more useful for accelerated testing). The buprenorphine release is generally extraordinarily slow. A quick early release is observed in several cases, e.g. B3 and B4, and this release is hypothesized to be due to buprenorphine at or near the surface of the PLGA microparticles. The very low solubility and hydrophobicity of the buprenorphine molecule, coupled with the 85:15 PLGA, may require substantial degradation and/or erosion of the microparticle to release the interior buprenorphine.

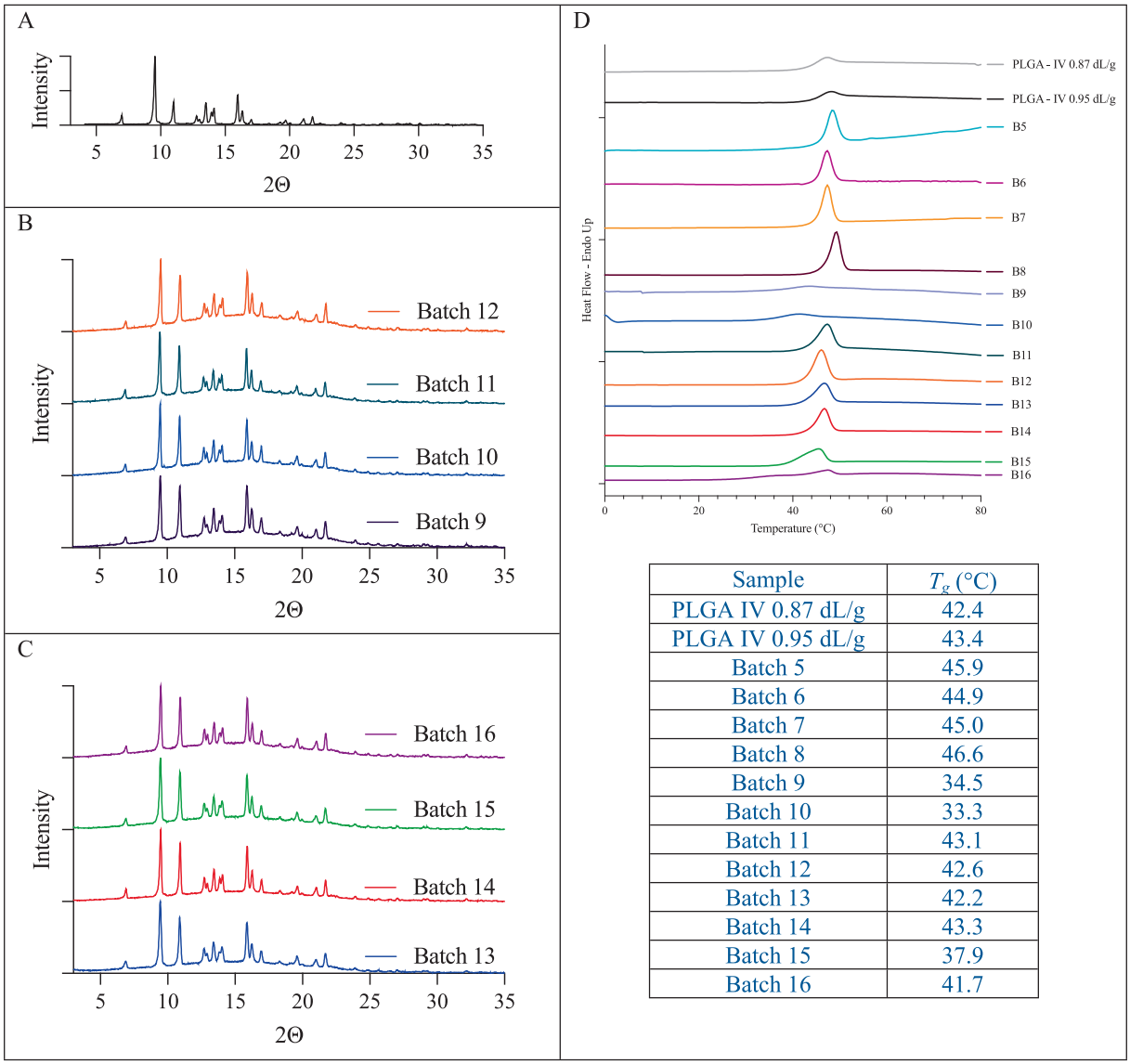
3.5. *In vivo pharmacokinetics in the rodent model*

A candidate formulation (B15) was selected for an *in vivo* study in the rodent model, based upon the drug loading (~41 %), encapsulation efficiency (~100 %), *in vitro* release rate, and processability of the PLGA concentration. A dose of 31 mg/kg was administered in the subcutaneous space with an aqueous diluent. This is a human equivalent dose of 300 mg, targeting a duration of ~ 3 months or 100 mg/month. Blood samples were taken from the lateral tail vein, and equivalent fluids (to the blood taken) were administered subcutaneously. Fig. 7 illustrates the plasma buprenorphine concentration over time of formulation **Batch 15**. The profile clearly demonstrates steady-state release with minimal to no burst release. The formulation maintains a level of $\geq$ 2 ng/mL for more than 60 days, and then slightly below 2 for the remaining 40 days of the study. These concentrations are above the minimum effective concentration of 0.7 ng/mL observed in Probuphine (FDA, 2016; Mumenthaler and Beebe, 2015) and around 1.25 ng/mL observed in the 1-month Brixadi formulation (Braeburn, 2023). The buprenorphine loading of this formulation is 40 %, greater than any currently approved FDA PLGA microparticle-based product. This demonstrates the potential of this technology to produce a future product. While the formulation development used a benchtop rotor–stator homogenizer, this formulation design could be readily transferred to an in-line type homogenizer for semi-continuous process development (Otte et al., 2023).

4. Discussion

4.1. *Cost of the opioid epidemic*

In 2020, 2.7 million people in the U.S. had an OUD (SAMHSA, 2021), significantly increasing from 1.6 million individuals in 2019. This drastic increase might have been affected by the COVID-19 epidemic, resulting in the risk of depression and increased barriers to care. The recent estimate of $35 billion in direct healthcare costs (PEW, 2021), let alone the estimated $1 trillion in overall societal cost (Florence et al., 2021)), indicate the potential savings that effective medications for opioid use disorder (MOUD) could provide. However, currently it is estimated that less than 20 % of the U.S. OUD population that could benefit is currently on treatments (Englander et al., 2024). A 3-month extended-release injectable buprenorphine could help address some of the underutilization of MOUD and help expand the treatment potential, saving lives and providing a better quality of life for OUD patients while ultimately saving healthcare and societal costs.



Sample	T_g (°C)
PLGA IV 0.87 dL/g	42.4
PLGA IV 0.95 dL/g	43.4
Batch 5	45.9
Batch 6	44.9
Batch 7	45.0
Batch 8	46.6
Batch 9	34.5
Batch 10	33.3
Batch 11	43.1
Batch 12	42.6
Batch 13	42.2
Batch 14	43.3
Batch 15	37.9
Batch 16	41.7

Fig. 5. PXRD patterns of buprenorphine free base (A), Batches 9–12 (B), and Batches 13–16 (C) and thermal analysis of Batches 5–16 and PLGA with IV 0.87 and 0.95 dL/g (D).

4.2. Current buprenorphine MOUD

Daily dose buprenorphine: There are four main products in this category (Subutex, Suboxone, Zubsolv, and Bunavail), either taken sublingually or buccally as buprenorphine has poor oral bioavailability. Subutex (buprenorphine tablets) was the first approved buprenorphine product for MOUD in the U.S., is the least expensive, and is still considered preferable to many OUD patients. However, the healthcare community has largely discontinued the use of Subutex due to the high diversion potential, especially for use as an injectable formulation, increasing the potential for illicit use. Subsequent formulations (Suboxone, Zubsolv, and Bunavail) added naloxone to combat diversion with the theory that naloxone would block opioid response for injection (Poliwoda et al., 2022). These products are widely utilized, have good cost-benefit analyses, and sufficient real-world data to support their use. The drawbacks are compliance concerns, especially in unhoused or other challenging populations, diversion potential (Larance et al., 2014), and frequent required clinic visits, often including treatment requirements such as urine drug tests to ensure compliance. Importantly, due to the daily compliance requirement and significant side effects, most notably tooth decay for long-term use (Aschenbrenner, 2022), these therapies have a lower utilization rate than is desirable, especially considering the data on cost-effectiveness.

Extended-release buprenorphine: There are currently two main U. S. products in this category (Sublocade and Brixadi), both injectable depot formulations designed to reside in the subcutaneous space (Chappuy et al., 2021). These products are based on *in situ* forming injectable (ISFI) depots using a solvent (1-methyl-2-pyrrolidone, NMP) dissolved degradable polymer (PLGA) and buprenorphine. Upon injection, the solvent rapidly dissolves into the surrounding interstitial fluid, and the PLGA and buprenorphine crash out of the solution, forming an amorphous depot. The slow dissolution of buprenorphine and degradation of the PLGA extend the release, maintaining a threshold dose for continuous craving control (Chappuy et al., 2021). The benefits of these formulations are fewer clinic visits, no diversion or illicit use potential, and fewer compliance concerns. However, the uptake of these formulations is considerably lower than the daily dose options for two primary reasons: cost and pain. The cost of these treatments is approximately three times higher than the daily dose formulations, negatively impacting the cost-benefit ratio (Flam-Ross et al., 2023). More importantly, these products are associated with severe pain on injection due to the NMP, a solvent, with potential health risks, approved for use in very

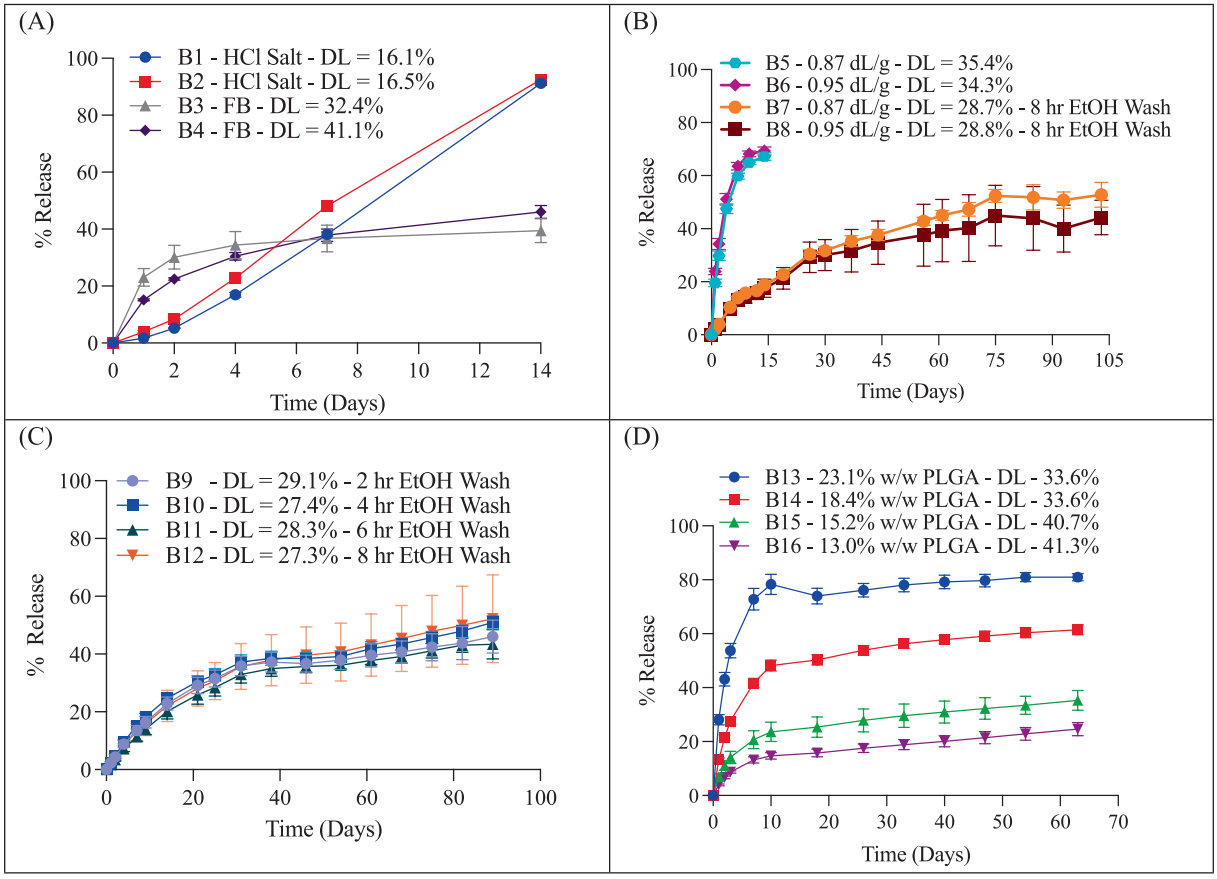


Fig. 6. In vitro buprenorphine release profiles of indicated microparticle batches.

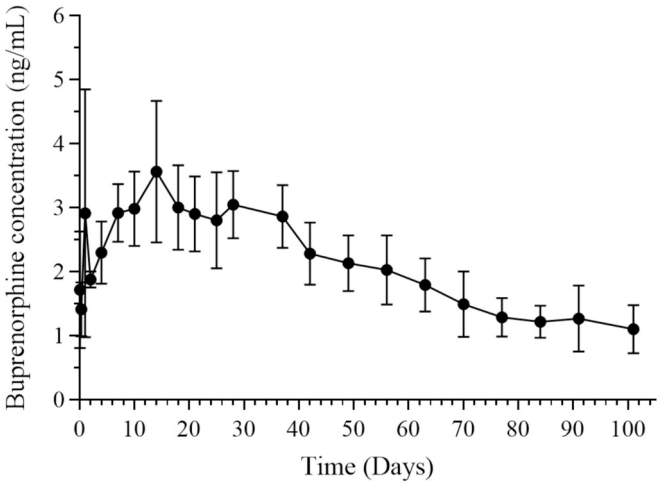


Fig. 7. Buprenorphine plasma concentration profile of Batch 15 formulation.

limited situations, partitioning into the local tissue and causing dehydration. The pain response has necessitated pain mitigation methods for delivery, such as the use of local analgesics, and has not only made OUD patients hesitant (to the level of claiming that this pain is intentional to punish PWUD (Bluelight.org, 2024), but also has negatively impacted the clinic's view on the use of these medications (Reddy et al., 2024; Weesner et al., 2022). With its recent approval, Brixadi use in the market is anecdotally considered an improvement over Sublocade, primarily due to enabling more injection sites, such as the upper arm, which is less sensitive to pain but still has the same potential drawbacks. Due to all these reasons, the long-term compliance with these medications is low, with OUD patients often dropping out of therapy or switching to daily buprenorphine or methadone. Combined with the high costs, this has resulted in a break-even cost-benefit ratio for these MOUD (Flam-Ross et al., 2023) further leading away from these being utilized.

4.3. Rationale for a microparticle formulation for long-acting buprenorphine delivery

There is significant interest in extended-release buprenorphine products as they can enable patients to "avoid the stigma of having to make daily trips to opioid agonist therapy clinics" (i.e., methadone and buprenorphine) and "having increased time to engage in activities such as travel, study, work or volunteering (Barnett et al., 2021)." Medication for opioid use disorder has been shown to increase treatment retention for OUD (Mattick et al., 2014), a reduction in illicit opioid use (Knittel et al., 2023), an improvement in neonatal outcomes for babies born to women with OUD (Knittel et al., 2023), a reduction in opioid-related mortality rates (Sordo et al., 2017), and a reduction in substantiated cases of child abuse and neglect (Morris et al., 2019). A recently approved competitor, Brixadi was estimated to be used in more than 7,000 US patients within 6 months after launch, demonstrating the clinical demand and need for new formulations to help tackle the opioid epidemic (Tiberg, 2024). Providing a number of formulation configurations will enable patients and providers alike varying options to tailor therapy to a patient's needs and recovery journey.

With the 1-month buprenorphine formulations available, the question may arise as to why ISF implants have not been used to deliver buprenorphine for more than one month. There are currently only 4 ISFIs approved by the FDA: Atridox® delivering doxycycline for 1 week, Eligard® delivering leuprolide up to 6 months, Sublocade® delivering

buprenorphine for 1 month, and Perseris® delivering risperidone for 1 month. However, buprenorphine has not been approved to deliver for 3 months using ISFI formulation. As evidence, the Eligard, a 6-month leuprolide formulation, delivers 400 times more drug on the first day than the steady-state dose (QLT-USA, 2007). For a 1-month Sublocade, the initial burst release results in a 4- to 6-fold peak concentration compared to the steady state, an acceptable if not ideal initial dose. However, if extended to 3-months, with the expected subsequent increase in burst release to considerably over 10-fold, the resulting initial dose would exceed the therapeutic range and would cause harm to the patient. Simply put, a 3-month buprenorphine formulation cannot be made by simply multiplying the 1-month ISFI dose 3 times.

A 3-month injectable buprenorphine microparticle formulation for intramuscular injection could provide MOUD with a therapeutic duration 3 times longer than a single subcutaneous injection of the current extended-release buprenorphine formulations, Sublocade or Brixadi. Importantly, this formulation could potentially minimize one of the biggest complaints of those competitors of severe pain on injection due to local dehydration and toxicity of the solvent (Reddy et al., 2024; Weesner et al., 2022). This could enable patients to be stable on therapy and reduce office visits, a means to keep those in rural areas with limited transportation on therapy longer, a more stable plasma concentration profile, and a reduction in the accumulation of plasma buprenorphine via less frequent administration. Daily dosed buprenorphine shows a lifetime cost benefit, saving healthcare costs and reducing lost productivity while improving long-term quality of life (Flam-Ross et al., 2023). However, this benefit disappears with the alternative current 1-month extended-release buprenorphine formulations due to multiple factors, including lower retention rates and significantly higher cost (Flam-Ross et al., 2023). The formulation described here has the potential to significantly improve the current options with a longer duration, lower cost, and fewer side effects, potentially resulting in higher compliance and retention.

4.4. Calculation of the minimum effective buprenorphine concentration in the plasma

It is estimated that signs and symptoms of opioid withdrawal may require $\geq$ 50 % μ opioid receptor occupancy (μORO), which is often related to $\geq$ 1 ng/mL buprenorphine concentrations in the plasma, while the opioid blockade requires buprenorphine concentrations $\geq$ 2 ng/mL (Lintzeris and Dunlop, 2019; Queensland-Health, 2019). Administration of Sublocade (300 mg dose followed by 100 mg dose) results in the buprenorphine plasma concentration $\geq$ 2 ng/mL (Jones et al., 2021). Such a high plasma level is understandable considering the high doses (100 mg or 300 mg/month) of buprenorphine.

Probuphine is effective in treating OUD and clinically similar to those receiving sublingual buprenorphine/ naloxone (Barnwal et al., 2017; Ling et al., 2019). The Probuphine implant is a subdermal poly (ethylene-co-vinyl acetate) device, measuring 26 mm in length and 2.5 mm in diameter, and containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride) per implant (Probuphine, 2016). It is administered as four implants for a treatment duration of six months. The pharmacokinetic data of Probuphine in clinical pharmacology and biopharmaceutics review(s) (FDA, 2016) is shown in Fig. 8. The dotted line in Fig. 8 shows the range of buprenorphine concentration after reaching the steady-state concentration 3–4 weeks after implant and was sustained over 6 months, averaging 0.72 ng/mL for the 4 implants (FDA, 2016; Mumenthaler and Beebe, 2015). The minimum effective buprenorphine concentration achieved by Probuphine appears to be 0.7 ng/mL. The minimum plasma buprenorphine level is not the only factor accounting for the clinical effects but provides the basis for calculating the total buprenorphine dose necessary for a 3-month PLGA microparticle formulation.

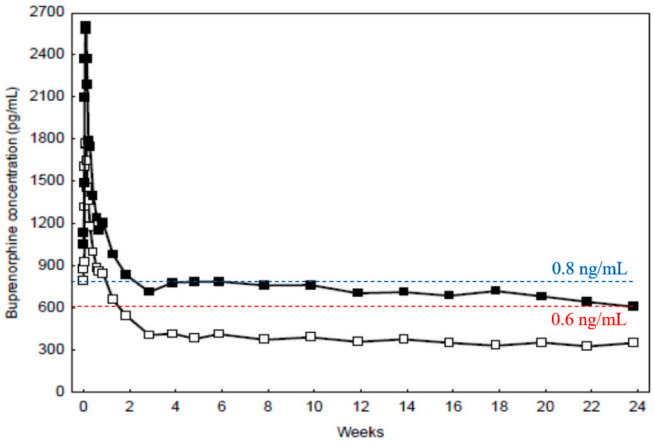


Fig. 8. Mean plasma buprenorphine concentrations for dose Groups A (□, 2 Probuphine implants) and B (■, 4 Probuphine implants) after Probuphine insertion. (From (Probuphine, 2016), the dotted lines are added for emphasis).

4.5. Buprenorphine PLGA-based microparticle formulation

PLGA microparticles can be prepared by various methods including oil-in-water emulsification (O/W), or water-in-oil-in-water (W/O/W) emulsification, solid-in-oil-in-water (S/O/W) emulsification, membrane emulsification, microfluidics, spray drying, and coaxial spraying (Lee et al., 2019; Nkanga et al., 2020; O'Brien et al., 2021). Of these, O/W or W/O/W emulsification has been used for most FDA-approved PLGA microparticle products. Microparticle formulations can be made to minimize the initial burst release and are good formulations for up to 3-month delivery. However, there are many parameters to be controlled, and the scale-up manufacturing process is complex. Considerations include solubility of the drug in water and oil solvents, compatibility of the drug with PLGA, choice of oil solvents, as well as emulsification technique, and post-emulsification processes.

Buprenorphine is a nucleophilic drug, just like naltrexone and risperidone, in organic solvents. Thus, buprenorphine is expected to cleave ester bonds of PLGA polymers (Sharifi et al., 2020). Thus, it is vital to evaluate the molecular weight of the PLGA used before and after preparing microparticles. Additionally, buprenorphine base has an exceedingly low solubility in water and most organic solvents. As such, we decided to utilize solid buprenorphine crystals suspended in an oil phase containing the PLGA, emulsified in an aqueous phase. As a predominant portion of buprenorphine is not molecularly dispersed in the polymer matrix, it is hypothesized the amount and/or rate of nucleophilic cleavage is expected to be low and/or slow. This S/O/W technique for microparticle formation resulted in superior control over loading and microparticle size while maintaining PLGA integrity. The resulting *in vitro* and *in vivo* assays demonstrated excellent release kinetics easily matching our targets. This 3-month extended-release buprenorphine PLGA microparticle would be a worthwhile addition to the medicine landscape for treating OUD.

CRediT authorship contribution statement

Andrew Otte: Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chad Johnson:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **John Garner:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Kinam Park:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.126006.

Data availability

Data will be made available on request.

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