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Compacted solid implant formulations for long-term buprenorphine delivery☆,☆☆

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ABSTRACT

Opioid use disorder (OUD) remains a major public health challenge in the United States, and medication-assisted treatment with buprenorphine, a μ-opioid receptor partial agonist, is a cornerstone of effective management. Currently marketed long-acting buprenorphine products provide drug release for 1 week or 1 month. Here, we describe the development of new biodegradable PLGA rod formulations capable of sustaining buprenorphine release for ≥3 months.

Poly(lactide-*co*-glycolide) (PLGA) and buprenorphine free base were thermally compacted into solid rods using a plastometer at 165–180 °C under a compression load of 4–16 kg. A primary objective of this formulation strategy was to minimize the initial burst release characteristic of conventional PLGA systems by reducing interconnected pore formation through compaction. The resulting implants contain 70% *w*/w buprenorphine and are straightforward to manufacture.

In vivo pharmacokinetic evaluations in both rat and dog models demonstrated sustained plasma buprenorphine concentrations for more than 3 months. These long-acting implants may provide extended therapeutic coverage compared with existing products, potentially improving patient adherence and clinical outcomes in OUD treatment.

1. Introduction

1.1. Opioid use disorder and buprenorphine

Opioid use disorder (OUD) remains a significant public health crisis in the United States, with substantial consequences for individuals, families, and communities. Although drug overdose deaths decreased from 114,000 in 2023 to approximately 87,000 in 2024 [1], the annual mortality burden remains unacceptably high. OUD is commonly treated with medications such as buprenorphine, methadone, and naltrexone [2]. Buprenorphine is a partial agonist at the μ-opioid receptor, whereas methadone is a full agonist at the μ-, κ-, and δ-opioid receptors, carrying a greater risk of respiratory depression and certain mental health complications relative to buprenorphine [3,4]. Naltrexone, by contrast, is a pure opioid antagonist. Because the FDA continues to encourage the development of new evidence-based treatments for OUD [5], buprenorphine was selected as the therapeutic agent for this formulation development study.

FDA-approved buprenorphine products for OUD include oral formulations—sublingual tablets (Subutex® and Zubsolv®) and oral films (Suboxone® and Bunavail®)—as well as long-acting injectables, namely the 1-month PLGA-based Sublocade® and the 1-month liquid-crystal formulation Brixadi®. [6]. A 6-month implantable formulation, Probuphine®, composed of a non-biodegradable ethylene-vinyl acetate copolymer, was removed from the market in 2020 due to limited adoption [7,8]. Its primary limitation was the requirement for surgical insertion and removal. Consequently, next-generation long-acting buprenorphine formulations should employ biodegradable polymers, eliminating the need for surgical explantation at the end of dosing.

1.2. PLGA-based long-acting injectable (LAI) formulations (Sublocade)

Sublocade® is composed of buprenorphine and PLGA 50:50 (lactide: glycolide = 50:50) dissolved in *N*-methyl-2-pyrrolidone (NMP) and delivers 100 mg (0.5 mL) or 300 mg (1.5 mL) of buprenorphine over one month [9]. Another long-acting buprenorphine depot, Norvex™, was

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developed using drug-loaded PLGA microparticles coated with an additional PLGA membrane to prolong release [10]. The formulation contained 58 mg buprenorphine with a targeted delivery rate of 1.45 mg/day for 40 days. However, in a human pharmacokinetic study, mean plasma buprenorphine concentrations declined below 0.6 ng/mL after approximately 20 days. The Norvex formulation might have been further optimized, for example, by reducing the initial burst release or increasing drug loading, to achieve a clinically useful 1-month duration.

There remains a need for new PLGA-based long-acting buprenorphine formulations capable of delivering the drug for longer than one month to improve patient convenience and adherence. A depot capable of sustaining release for three months or more (≥3 months) would be particularly advantageous for OUD treatment. This depot could be in the form of a long-acting injectable, microparticle suspension of in situ-forming depot, that may be injected subcutaneously or intramuscularly sustaining therapeutic plasma concentration for ≥3 months. Recently, a PLGA microparticle formulation was reported that maintained buprenorphine plasma concentrations above 1 ng/mL in male Sprague–Dawley rats for over 100 days [11]. Alternatively, this could be formulated as an implant, preferably a cylindrical rod to facilitate administration, consisting of a solid, pre-formed system placed in the subcutaneous or subdermal space.

1.3. Liquid crystalline-based long-acting injectable formulations (Brixadi)

Brixadi is a long-acting buprenorphine formulation that uses FluidCrystal® injection depot technology, in which buprenorphine is dissolved in a lipid-based liquid that spontaneously forms a nanostructured liquid-crystalline gel upon contact with subcutaneous fluids, encapsulating the buprenorphine and subsequently releasing it at a controlled rate [12]. The weekly composition consists of anhydrous ethanol and soybean phosphatidylcholine/glycerol dioleate, whereas the monthly formulation contains NMP and soybean phosphatidylcholine/glycerol dioleate [13]. Brixadi weekly and monthly formulations are supplied in 4 dose strengths each, with peak concentrations observed about 6–10 h for the monthly doses, and after 24 h for the weekly. Clinical data support Brixadi's efficacy: in a pivotal Phase 3 trial, weekly or monthly Brixadi was non-inferior to daily sublingual buprenorphine/naloxone in suppressing illicit opioid use, as measured by urine drug screens and self-reported use [14]. Brixadi was generally well tolerated, with a systemic safety profile similar to sublingual buprenorphine/naloxone. Despite these advantages, Brixadi's dosing interval remains limited to weekly or monthly, underscoring an unmet need for buprenorphine formulations that sustain therapeutic levels for longer periods (e.g., ≥ 3 months), which could further enhance adherence and patient outcomes.

1.4. Non-erodible buprenorphine implants (Probuphine)

Each Probuphine implant is a soft, flexible, rod-shaped ethylene-vinyl acetate implant that is 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride) [15]. After insertion of the rods (4–5 rods), an initial pulse release is observed, followed by constant release until the rods are removed at 6 months [16]. A reduction in the risk of diversion, improved patient compliance, minimizing the daily peaks and troughs, thus reducing overall drug exposure, were some of the anticipated advantages over sublingual preparations [17]. Fewer than one in ten of those who attended the implant procedure training administered a single implant [17]. The required removal further complicated potential clinical implementation and contributed to the ultimate market removal.

1.5. A new ≥3-month buprenorphine delivery system: compacted rod formulations

In addition to PLGA microparticle formulations, a new approach has been explored in this study to develop formulations with buprenorphine delivery lasting ≥3 months, with a specific focus on reducing the initial burst release, increasing the drug loading up to 70% *w*/w of the total weight of the formulation, and using a biodegradable formulation. Previous research has shown that the initial burst release is likely due to the convective water absorption into PLGA formulations through interconnected pores [18–21].

Interconnected pores typically form during the removal of water and solvent during microparticle preparation and during the phase inversion process used for in situ-forming implants. Preventing the development of these interconnected pores remains challenging. For example, a combined phase inversion–compaction process was employed for a dolutegravir implant [22]. However, implementing this approach at commercial scale may be difficult due to its multistep nature—particularly the phase inversion step coupled with residual solvent and water removal, followed by compaction. Solid implants offer the advantage of higher drug loadings, potentially longer therapeutic durations, and fewer doses, due to a combination of the higher obtainable solid fractions, minimal porosity, and implant geometry/size. A drawback of these systems, as noted in the Probuphine case, is the relative size and/or number of implants required for the desired therapeutic outcome; ultimately, an outpatient procedure may be necessary for implantation. Nexplanon and Vantas are two examples of geometrically similar implants (cylindrical rod-shaped, although each only requiring a single rod), with demonstrated clinical utility based upon their long-standing commercial success to date [23,24]. Therefore, a single biodegradable rod system providing ≥3 months may ultimately provide demonstrable therapeutic benefits and be clinically feasible for patients working to overcome opioid use disorder.

2. Materials and methods

2.1. Materials

Buprenorphine HCl was obtained from SpecGx, LLC. PLGA 85:15 was obtained from Ashland. The inherent viscosities (IV) of PLGA-ester endcap 75:25 was 0.21, while PLGA 85:15 were 0.28 and 0.82 dL/g.

2.2. Preparation and solubility measurement of buprenorphine free base (FB)

Buprenorphine free base (FB) was created by dissolving buprenorphine HCl in water with 3% *v*/v methanol to obtain a 1.3% solution. Buprenorphine FB was precipitated with excess NaOH. Dichloromethane at a 13% v/v ratio was then added to dissolve the precipitated buprenorphine, and subsequently, a liquid-liquid extraction was performed to remove the dichloromethane-buprenorphine solution. The dichloromethane was subsequently removed under vacuum over 48 h, yielding buprenorphine FB.

The solubility of buprenorphine FB was determined in PBS with 0.05% Tween 20 (PBST) and 0.5% *w/v* sodium dodecyl sulfate (SDS) in water. The solubility was determined by placing excess buprenorphine FB into the media mentioned above at 37 °C and shaking at 40 RPM for 48 h. After 48 h, a sample was taken and centrifuged at 15,000 RPM for 5 min. The supernatant was collected and diluted with the same medium, and the concentration was determined by high-performance liquid chromatography.

2.3. Preparation of buprenorphine powder

Buprenorphine powder was prepared via mortar and pestle. Buprenorphine crystals were placed in the mortar and lightly ground with the pestle for ~5 min. The ground buprenorphine was then passed through a 150 μm sieve and collected for use.

2.4. X-ray powder diffraction

X-ray powder diffraction (XRD) was used to identify crystalline buprenorphine. The data were collected on a Panalytical Empyrean X-ray diffractometer equipped with Bragg-Brentano HD optics, a sealed tube copper X-ray source (= 1.54178 Å), Soller slits on both the incident and receiving optics sides, and a PixCel3D Medipix detector. Samples were packed into metal sample cups with a 16 mm-wide and 2 mm-deep sample volume. 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.

2.5. Preparation of PLGA powder

PLGA is typically supplied as large granules, often larger than the 2.095 mm orifice used for ASTM test D1238 on the plastometer. To facilitate thorough mixing with buprenorphine, smaller PLGA particles were prepared by cryo-milling. A Retsch CryoMill was used to prepare PLGA particles of various grades of ester end-capped PLGA. About 10 mL of tapped PLGA granules was measured volumetrically and placed into a 25 mL stainless steel CryoMill jar with 10 stainless steel media balls (8 mm diameter). The jar was precooled for 10 min, followed by 6 cycles of 10 min of milling at 30 Hz, with an immediate 1-min intermediate cooling time between each cycle. The ground PLGA was allowed to equilibrate to room temperature, then passed through a 150 μm sieve and collected for use.

2.6. Particle size measurement

The particle size distribution was measured using a CILAS 1190 particle size analyzer. Approximately 50 mg of buprenorphine free base or PLGA powder was dispersed in 1.5 mL of a 0.1% Tween 80 aqueous solution, and the mixture was subsequently analyzed.

2.7. Preparation of compacted buprenorphine/PLGA rod formulation

Compacted rod-shaped formulations were manufactured using a plastometer (Tinius Olsen MP1200) with slight modifications to the die geometry. A plastometer is also referred to as an extrusion plastometer or a melt flow index tester. A plastometer consists of a barrel with a heating chamber where the polymer sample is placed, heated to temperatures below the melting temperatures of PLGA and buprenorphine but above the glass transition temperature of PLGA (Fig. 1). A piston is used to apply a specific amount of pressure to the melted polymer in the barrel. The pressure forces the polymer through a small die orifice placed at the end of the barrel. The force applied by the piston is constant, and the subsequent flow of the polymer is measured. In this example, the barrel temperature was always lower than the melting temperatures of the drug and polymer in the formulation. The precompaction load, compaction load, die orifice and length, barrel temperature, and barrel diameter were adjusted in the plastometer according to the respective formulation being prepared.

Compacted buprenorphine rods were prepared using a plastometer. Buprenorphine free base powder (70% *w*/w) was blended with PLGA powder (30% w/w) with a Resodyn acoustic mixer for 1 min. Magnesium stearate (0.5% w/w) was added, then mixed in the Resodyn mixer at the same settings for 5 min. A die with an orifice of 3.5 mm was used for the rod preparation. One gram of material was loaded into the plastometer, set to a predetermined temperature (165 or 180 °C), and the die was plugged. The precompaction temperatures were all below the melting point of the drug (~217 °C). The piston was then inserted into the heated barrel, and a precompaction weight of 16 kg was applied for 3 min. This precompaction weight eliminated air pockets from the powder mixture, creating a solid entity. This temperature range was chosen to be well below the melting temperature of buprenorphine, with an intentionally shorter thermal residence time to minimize degradation risk, while also maximizing consolidation of the buprenorphine-PLGA mixture. Buprenorphine has previously been processed using thermal methods, including hot-melt extrusion and solid-state polymer processing, under comparable or more severe thermal conditions without evidence of significant chemical degradation [25]. In general, drug substances processed by melt extrusion generally retain chemical stability when processed below melting/degradation temperatures and with short residence times [26]. The precompaction weight was removed, followed by the die plug, and then a weight was applied to generate a buprenorphine-loaded rod. The temperature and weight were chosen to provide a similar rod flow rate across formulations. The specific processing and formulation parameters are summarized in Table 1. This preliminary study focused on two relevant L:G ratios (75:25 and 85:15), selecting polymers with low inherent viscosities (~0.2–0.3 dL/g) for both ratios and a higher inherent viscosity (~0.8 dL/g) for the 85:15 polymer. These polymers were chosen based on their prior use in long-acting delivery systems with durations of one month or longer and to span a broad design space, enabling evaluation of a wide range of release performance attributes. The rods were allowed to cool to room temperature and then cut to size. (See Fig. 1.)

2.8. In vitro buprenorphine release

The shake-flask method was used to characterize the in vitro release kinetics [27]. Buprenorphine rods were each placed individually in 125 mL Erlenmeyer flasks sealed with a rubber stopper. Due to the extremely low aqueous solubility of buprenorphine free base, in vitro release testing was conducted in 50 mL of 0.5% sodium dodecyl sulfate (SDS) at 37 °C [28]. At each time point, the entire 50 mL of release medium was replaced with fresh medium to maintain a sufficient sink. Buprenorphine concentrations in the release medium were quantified by HPLC.

2.9. High performance liquid chromatography

Buprenorphine quantitation was performed using an Agilent 1260 HPLC system equipped with a UV absorbance detector. Chromatographic separation was achieved on a Zorbax SB-C18 column (150 × 4.6 mm, 5 μm) maintained at 30 °C. The mobile phase consisted of acetonitrile and 10 mmol potassium phosphate buffer (83:17, *v*/v; pH 6.0) delivered at a flow rate of 1.0 mL/min. The autosampler was operated at ambient temperature. UV detection was performed at 210 nm. The injection volume was 2.5 μL for drug-loading samples and 20 μL for in vitro release samples. The total run time was 10 min, with buprenorphine eluting at approximately 7.6 min.

2.10. In vivo pharmacokinetic studies

Institutional Animal Care and Use Committee approval was obtained for all animal procedures. Sprague–Dawley rats (Envigo, Indianapolis, IN) were acclimated for one week prior to dosing. A small area in the dorsal scruff region was shaved, and a ~ 5 mm incision was made with an 11-scalpel blade while under anesthesia. Buprenorphine rods (30, 60, or 120 mg/kg; $n = 3$ per group) were implanted into the dorsal region using a 3.5 mm trocar and cannula under aseptic conditions. The incision was closed with surgical glue. Rats were anesthetized for serial blood collection (~250 μL) via the tail vein over a 112-day study period.

Table 1
Three buprenorphine rod formulations characterized.

Formulation ID	L:G ratio	Inherent Viscosity (dL/g)	Temperature (°C)	Applied weight during rod formation (kg)
F75–0.21	75:25	0.21	180	4
F85–0.28	85:15	0.28	165	6
F85–0.82	85:15	0.82	180	10

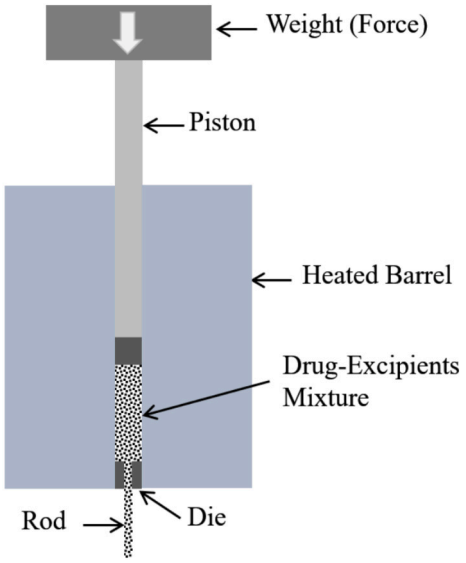

Fig. 1. A schematic diagram of buprenorphine/PLGA rod formation using a plastometer. Both buprenorphine and PLGA are heated below their melting temperatures but above the PLGA glass transition temperature.

Blood samples were collected into labeled potassium EDTA tubes and centrifuged at 5000 rpm for 10 min at 4 °C. Plasma was transferred into labeled 1 mL plastic tubes and stored at −80 °C until analysis. After completion of the pharmacokinetic portion, rats were euthanized, and the residual buprenorphine implants were explanted.

Compacted buprenorphine rods (250 mg buprenorphine; $n = 4$ per formulation) were evaluated in beagle dogs. The implant site was shaved, and a small incision was made in the dorsal scruff region using an 11-blade scalpel in an area that minimized the dogs' ability to scratch. Implantation was performed using a stainless steel 3.5 mm sharp obturator with a diamond-tip protector and cannula, followed by placement with a 3.5 mm trocar (blunt obturator) into the dorsal scapular region. After removal of the trocar and cannula, the incision was closed with tissue adhesive as needed. Blood samples were collected from the jugular or cephalic vein into K_2EDTA tubes. Samples were kept chilled, centrifuged in a refrigerated centrifuge at approximately 3500 rpm (260 *g*) for 10 min at 4–8 °C, and the resulting plasma was stored at −70 °C until analysis. Following the Day 120 blood collection, implants were aseptically explanted under sedation, and the incision was closed with tissue adhesive or sutures.

2.11. Buprenorphine plasma analysis

Buprenorphine was analyzed by liquid chromatography mass spectrometry. A stable labeled deuterated analog of was used as an internal standard and for quantitation. Buprenorphine-D_4 was purchased from Sigma Aldrich (St. Louis, MO). The plasma calibration curve ranged from 0.2 to 100 ng/mL. Plasma samples were stored at −80 °C until analysis. The plasma was thawed and 0.1 mL aliquoted into a tube for buprenorphine extraction. 5 ng/mL of buprenorphine-D_4 was added to each sample before extraction. Each sample was extracted with a 5× volume of methyl tert-butyl ether (MtBE). After vortexing for 10 min, the samples were centrifuged at 13,000 rpm for 10 min. The supernatant was collected, transferred to a new tube, and dried using a rotary evaporation device. The samples were subsequently reconstituted in 0.1 mL of 5% acetonitrile +0.1% formic acid prior to LC/MS/MS analysis. The analysis was performed using a Sciex Exion liquid chromatography system coupled to a Sciex 5500 Triple Quad mass spectrometer. Reverse-phase chromatography was used with a Restek Raptor Biphenyl column (2.7 × 30 mm, 2.1 μm) for separation. A gradient mobile phase consisted of water +0.1% formic acid and acetonitrile +0.1% formic acid.

2.12. Statistical analyses

Experimental data were plotted and analyzed using GraphPad Prism software (version 10.6.1). Differences between more than two groups were assessed using one-way ANOVA with Tukey's post hoc test. The level of significance was set at $p < 0.05$.

3. Results

The solubility of buprenorphine FB was determined in PBS with 0.05% Tween 20 (PBST) and 0.5% *w/v* sodium dodecyl sulfate (SDS) in water. The solubility values determined in PBST and 0.5% SDS are 0.012 ± 0.002 mg/mL and 0.416 ± 0.003 mg/mL, respectively. Based on the PBST value, this corresponds to a practically insoluble or insoluble level per USP [29]; potentially advantageous from a long-acting delivery standpoint. Fig. 2 illustrates the powder X-ray diffraction patterns from the CSD compared to the HCl and FB forms used in this study. No observable differences are noted in the FB pattern relative to that obtained from the CSD, demonstrating that the conversion and recrystallization did not generate any polymorphic or solvated forms.

As previously noted, fine buprenorphine was prepared via mortar and pestle, while PLGA powder was prepared via cryomilling. This size distribution was selected based on the relatively high yield obtained from this material in previous internal studies. Similar-sized distributions of the two materials were also chosen, as different-sized particles are generally more prone to segregation, whereas similar-sized particles tend to mix well and remain uniform [30,31]. The particle size distributions (PSDs) of representative PLGA samples are shown in Fig. 3. In general, the PSDs are largely normal distributions. Some fines are noted in the distributions because a lower sieve cutoff was not used. Also, some larger than 150 μm are found in the distribution due to the irregularity of particles (aspect ratios $>>1$).

A decrease in the relative drug release rate with increasing system diameter was demonstrated in a PLGA-based system with ibuprofen at ~12% *w*/w loading, where increasing diffusional path lengths must be overcome for dissolution and release [32]. The dependency of size vs release has also been shown for PLGA-based microparticles of naltrexone, gefitinib, felodipine, and lidocaine [33–36]. In general, drug loading decreases as particle size decreases, due to an increase in the surface area to volume ratio. Smaller particles have a higher interfacial area in contact with the continuous phase, ultimately leading to preferential drug loss at or near the surface due to their much shorter diffusion path. This disproportionately affects smaller droplets because a larger fraction of their total drug content resides within the diffusional distance of the interface. For microparticles in general, the drug is typically the minor component of the matrix, accounting for less than 40% of the total weight. Here, buprenorphine is the major component at ~70% *w*/w, but has a drastically lower surface area to volume ratio than

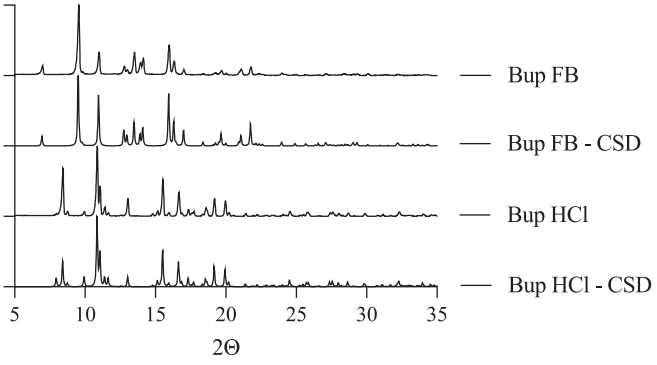

Fig. 2. Powder X-ray diffraction patterns of buprenorphine HCl from the Cambridge Structural Database (CSD), buprenorphine HCl tested as received, buprenorphine free base (FB) from the CSD, and buprenorphine FB prepared.

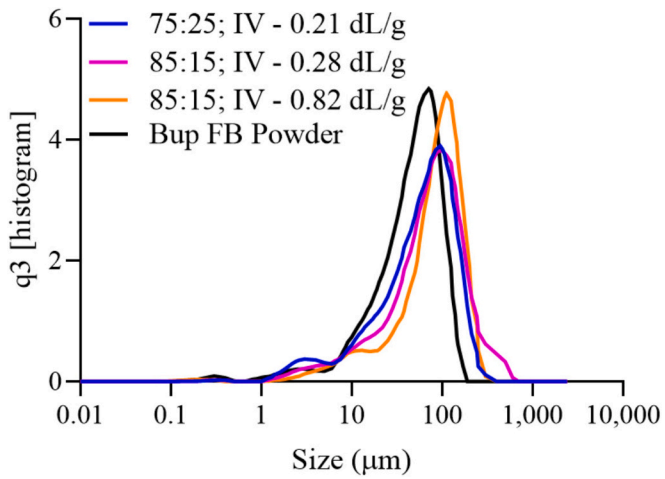

Fig. 3. The particle size distribution of cryo-milled PLGA and buprenorphine free base.

microparticles.

The release profiles of buprenorphine are plotted in Fig. 4. As previously noted, this test was performed in 0.5% SDS due to the poor solubility of buprenorphine, where these release profiles would arguably be considered on the aggressive side. For all three polymers characterized, the 30 mg/kg implant resulted in the fastest release kinetics, with overall kinetics decreasing as the dose (i.e., length) increased. In the F85–0.28 60 and 120 mg/kg implants, release appears to plateau significantly lower than anticipated. Whether this instance is due to experimental error during media removal and replacement or another unknown error is in question. The 75:25 polymer-based implants exhibit a triphasic release profile, whereas the two 85:15 profiles show biphasic behavior. This may be due to slight manufacturing differences among the three implant types, differences in degradation behavior between the 75:25 and 85:15 polymers, the aggressive dissolution conditions, or a combination of these factors.

Compacted buprenorphine rods (30, 60, or 120 mg/kg buprenorphine, $n = 3$/dose) were placed in the subcutaneous space in the dorsal scruff region in the rodent model via trocar and cannula to characterize the impact of dose size on the respective pharmacokinetics. Currently, there is no standardized definition of burst release. However, it generally refers to an initial, rapid release of a substantial fraction of the total amount of the loaded drug [37]. This phenomenon typically occurs within minutes to hours, whereas the total intended duration of drug delivery may extend over weeks and months. The formulations tested generally have minimal early plasma concentration spikes, followed by relatively steady-state plasma concentrations throughout the study. Some variability is present in the profiles, such as in formulation F85–0.82120 mg/kg (Fig. 5). Two peaks in the profile are found (around day 20 and days ~70–80), hypothesized to be random and general variability observed in in vivo testing.

The respective areas under the curve (AUCs) for the three formulations and dose levels are presented in Table 2. The highest buprenorphine exposures were observed with the F75–0.21 formulation across all doses, with exposure generally correlating with L:G ratio and IV. Notably, no difference in exposure was observed between the 30 and 60 mg/kg doses for F75–0.21 or F85–0.28, whereas a clear difference was detected for F85–0.82. Importantly, dose proportionality was not observed for any of the three formulations, which is hypothesized to result from differences in surface area-to-volume ratio across dose levels.

After 112 days, the implanted rods were explanted and analyzed to quantify the residual buprenorphine. The calculated remaining drug content is summarized in Table 3. A substantial fraction of the initially loaded buprenorphine remained at explantation, particularly in the 120 mg/kg dose groups. Gross examination at explantation showed that the implants remained largely intact, with reduced volume and no evidence of discoloration. A localized foreign body response was observed, requiring limited excision of surrounding tissue to facilitate implant removal. Overall, the amount of residual drug generally correlated with the calculated AUCs and corresponding dose levels. These findings indicate that a considerable proportion of the drug depot persists beyond 112 days, suggesting that the pharmacokinetic duration of this formulation could be extended further, provided therapeutic plasma

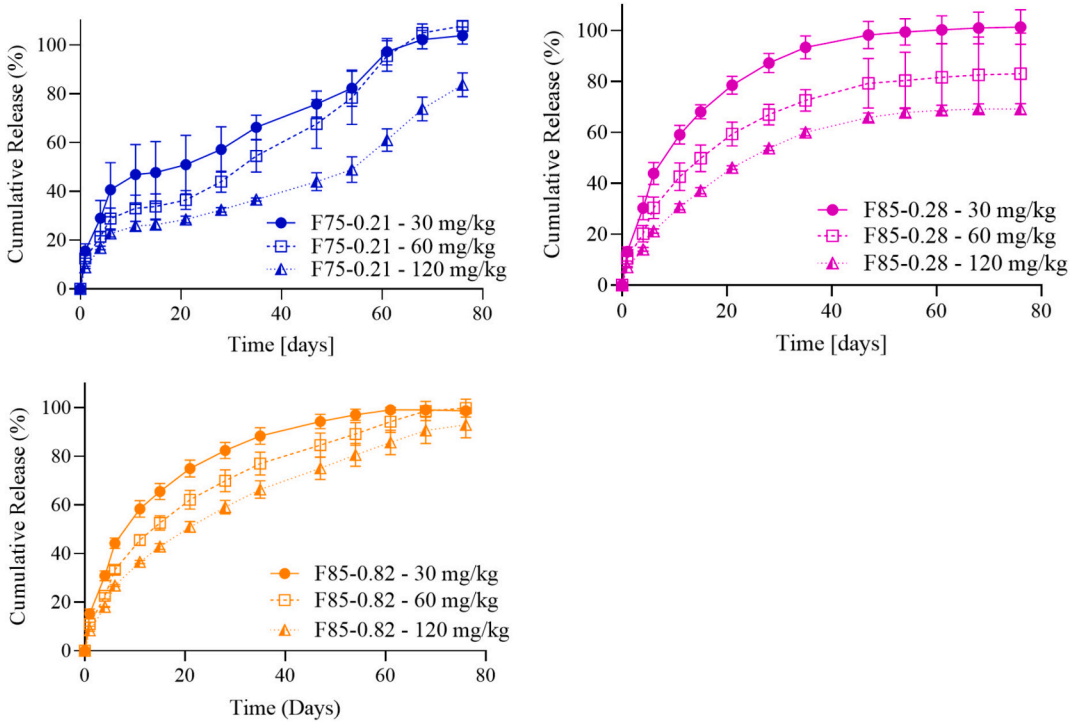

Fig. 4. In vitro buprenorphine release profiles of the buprenorphine rods from Table 1.

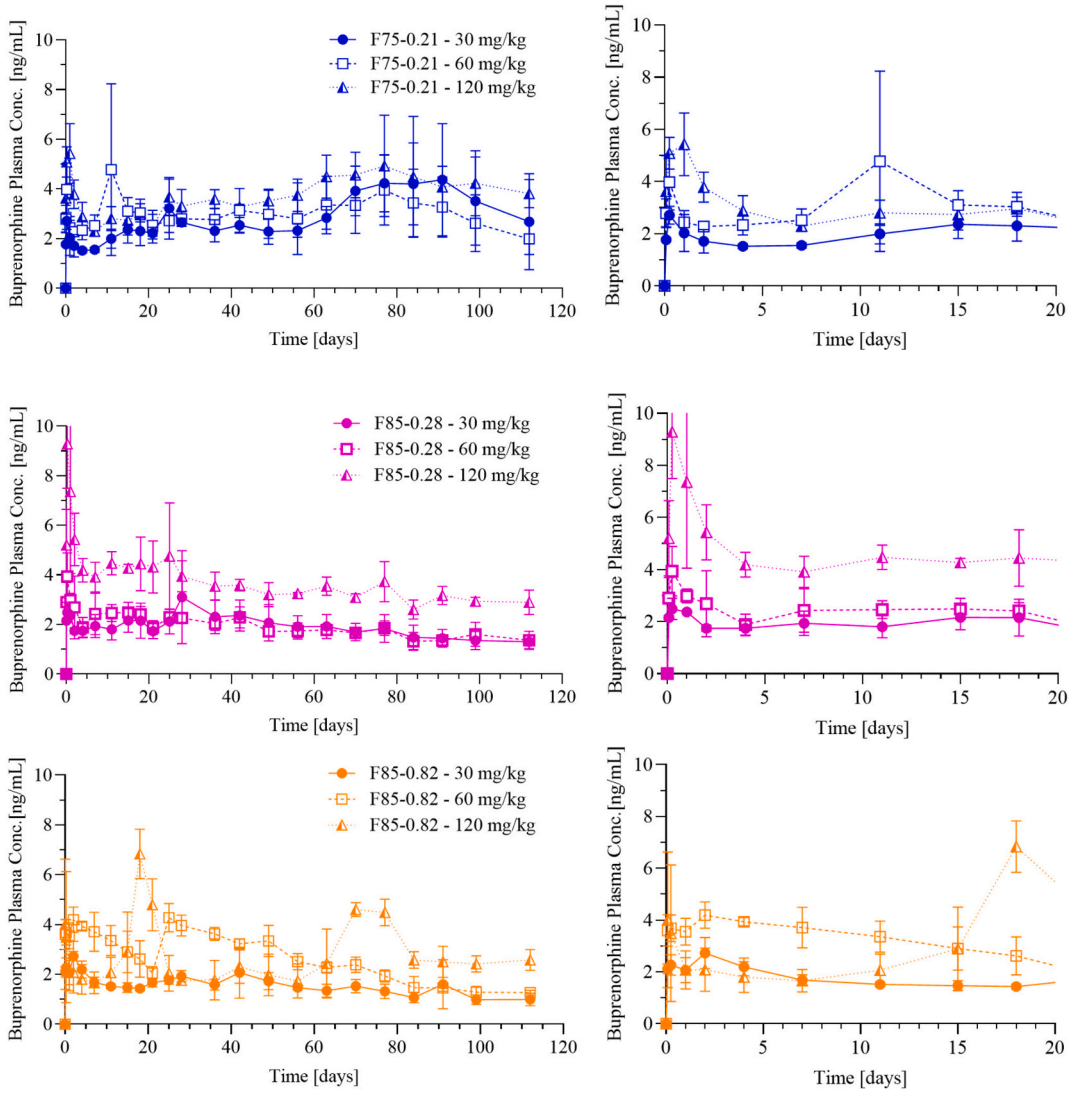

Fig. 5. Rodent pharmacokinetic profiles of buprenorphine rods as a function of dose.

Table 2
The respective $AUC_{d0–112}$ [ng·day/mL] for three formulations.

Dose (mg/kg)	F75–0.21	F85–0.28	F85–0.82
30	330.1 ± 44.0	210.5 ± 21.1	169.5 ± 14.4
60	339.0 ± 38.4	210.3 ± 11.7	286.5 ± 12.1
120	424.2 ± 37.3	400.7 ± 18.5	303.0 ± 23.0

The value listed is the average ± standard deviation.

Table 3
The residual buprenorphine (%) remained in the recovered rods.

Dose (mg/kg)	F75–0.21	F85–0.28	F85–0.82
30	46.3 ± 11.8	78.5 ± 9.7	67.2[#]
60	72.0 ± 5.1	79.0 ± 1.9	84.7 ± 3.4
120	81.8 ± 1.7	91.6 ± 1.2	90.0 ± 2.5

The value listed is the average ± standard deviation.
[#] $n = 2$.

concentrations can be maintained. Local tissue responses at the implantation site were not formally evaluated in the present study. Future investigations will assess tissue response as a function of dose and formulation. Notably, multiple clinically approved products have employed PLGA at comparable polymer concentrations and buprenorphine at similar dose levels (e.g., up to 300 mg). This existing clinical precedent supports the feasibility of achieving acceptable local safety profiles in future pre-preclinical safety studies.

Following the rodent results, a proof-of-concept study was conducted in dogs using a clinically relevant 250 mg dose delivered in a single buprenorphine rod. The pharmacokinetic profiles of formulations F75–0.21, F85–0.28, and F85–0.82 are shown in Fig. 6. Minimal to no visual differences were observed among the three formulations. After an initial burst release that produced plasma concentrations slightly above 2 ng/mL, levels declined over the first 4–5 weeks, followed by a steady-state phase that persisted until study completion. At Day 105, the rods were explanted and analyzed for residual buprenorphine. The residual drug content and corresponding AUC values are summarized in Table 4. Analysis of variance indicated no statistically significant differences in AUC among the three formulations. Consistent with the rodent study, a substantial amount of buprenorphine remained in the rods at the end of the study, highlighting the potential to extend the duration of release or adjust the formulation to achieve higher sustained plasma concentrations.

The initial burst release commonly observed in long-acting PLGA formulations is driven by rapid water ingress into the polymer matrix, followed by the swift release of drug located near or within surface-

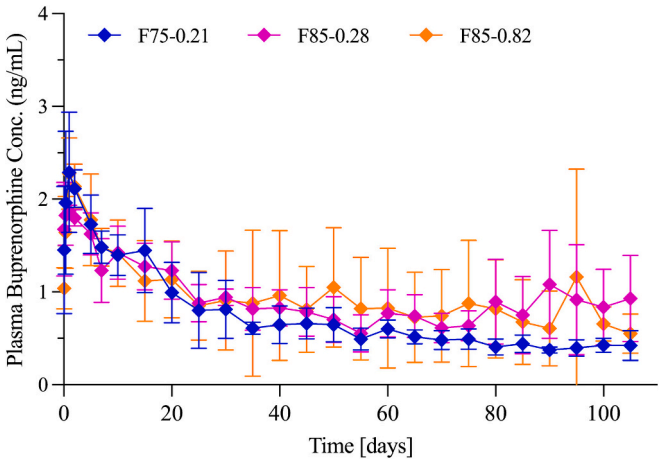

Fig. 6. Pharmacokinetic profiles of buprenorphine rods in Table 1 tested in dogs.

Table 4
Three buprenorphine rod formulations used in the dog study.

Formulation ID	$AUC_{d0–112}$ [ng·day/mL]	Remaining Buprenorphine (%)
F75–0.21	78.1 ± 6.6	80.8 ± 2.7
F85–0.28	97.6 ± 10.2	68.7 ± 15.0
F85–0.82	100.3 ± 17.9	75.1 ± 6.0

The value listed is the average ± standard deviation.

connected pores [18–21]. After this burst phase, the PLGA polymer chains undergo rearrangement at 37 °C, near their glass transition temperatures, forming a surface PLGA membrane that primarily governs steady-state drug release. The rapid uptake of water in most PLGA systems results from the presence of interconnected pores formed during solvent removal during typical PLGA microparticle manufacturing processes. Therefore, eliminating these interconnected pores may be essential to minimizing an uncontrolled initial burst release. Compaction of PLGA–drug powder mixtures may be a key strategy in achieving this outcome. Compacted buprenorphine–PLGA rod formulations have demonstrated minimal burst release, despite containing 70% drug by weight, followed by sustained plasma concentrations for more than three months.

4. Discussion

The mean steady-state plasma buprenorphine concentration achieved with Probuphine is approximately 0.5–1.0 ng/mL [38]. Probuphine is indicated for maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of buprenorphine [15]. In contrast, Sublocade achieves mean buprenorphine plasma concentrations of approximately 2 ng/mL and is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine product or who are already receiving buprenorphine therapy [9]. The pharmacokinetic profile of Sublocade demonstrates dose-dependent accumulation during the maintenance phase at 300 mg/month, whereas minimal accumulation is observed at the 100 mg/month maintenance dose [39].

Probuphine delivers 296.8 mg of buprenorphine over a six-month period, though at lower plasma concentrations than Sublocade. Extrapolating from these clinical benchmarks, a formulation designed to deliver buprenorphine over a three-month period could require as low as 150 mg to maintain a minimum plasma concentration C_{min} in patients stabilized on low-to-moderate doses of buprenorphine (0.5–1.0 ng/mL), and approximately 300 mg in patients being treated for moderate to severe opioid use disorder (~2 ng/mL) for a ≥ 3-month implant. Based on the pharmacokinetic profiles of buprenorphine rod formulations shown in Fig. 6, additional formulation optimization will likely be required to achieve plasma concentrations sufficient for the treatment of moderate to severe opioid use disorder. Potential strategies include using lower L:G ratio polymers, incorporating buprenorphine HCl, or including hygroscopic excipients (e.g., PEG) to enhance water uptake.

It is widely acknowledged that the L:G ratio of PLGA polymers directly influences degradation kinetics. For drug delivery durations exceeding three months, PLGA polymers with L:G ratios of 75:25 or higher are typically utilized. Ester end-group PLGAs are more hydrophobic than their acid end-group counterparts, and are therefore associated with slower water uptake and degradation. Polymer molecular weight is another critical parameter; higher molecular weight PLGAs and higher L:G ratios are generally associated with increased drug loading capacity, prolonged release profiles, and reduced initial burst release [40–44]. The optimal polymer content and molecular weight, drug content, and microstructure together determine the release kinetics of the formulation.

It should be noted, however, that these general trends are largely derived from studies of PLGA thin films or microparticles prepared using conventional emulsion-based methods. Whether these relationships translate directly to the compacted formulations described here remains to be determined. In the present study, PLGA type was selected to control the duration and kinetics of buprenorphine release based on prior experience. While sustained release over the intended duration was achieved, a substantial fraction of residual drug remained at the end of the study period. Accordingly, future work will investigate modifications to the L:G ratio to shorten the release duration and increase systemic exposure, while extending the pharmacokinetic evaluation period.

Interconnected pores may also form during hot-melt extrusion. As the drug–polymer mixture exits the die, the material expands due to polymer relaxation, a phenomenon known as die swell, resulting in a final diameter larger than the die orifice even after cooling [26]. Hot-melt extrusion has been widely used to produce PLGA-based solid implants, including Zoladex (10.8 mg goserelin acetate, 3-month duration), Ozurdex (0.7 mg dexamethasone, 3-month duration), Propel (0.37 mg mometasone furoate, 1-month duration), Scenesse (16 mg afamelanotide, 2-month duration), and Durysta (0.01 mg bimatoprost, 6-month duration). This process has also been applied to prepare high-loading buprenorphine implants (~47.5% *w*/w) using PLGA in combination with substantial amounts of a lubricant such as glyceryl monostearate (1–15% w/w) [25].

Heated compaction of drug–PLGA powders involves volume reduction through displacement of the gaseous phase, followed by particle deformation and consolidation into a single solid body. Additional excipients, such as binders, may be included to aid processing. The primary objective of heated compaction is to minimize porosity and open channels, induce entanglement of nearest neighbor polymer particles, thereby slowing water uptake and supporting sustained drug release over several months. Achieving an optimal compacted formulation requires careful selection of PLGA grades with appropriate particle size distributions and density relative to the punch-and-die dimensions. Furthermore, the drug's physicochemical properties largely influence the resultant performance. As previously noted, buprenorphine is characterized as insoluble, offering additional advantages. Due to its inherent partial agonist activity at the μ-opioid receptor, caution must be taken to minimize uncontrollable burst release due to potential side effects.

Compacted single-rod formulations offer several advantages: high buprenorphine loading (≥70%), controllable release kinetics, and a simplified manufacturing process that avoids polymer dissolution and solvent extraction. Compared to traditional emulsion-based PLGA microparticles, the compacted rod process involves far fewer variables, potentially enabling straightforward scale-up and lower manufacturing costs. The increased microstructural density of compacted rods slows

water ingress, reduces initial burst release, and supports prolonged drug release. Furthermore, if early discontinuation of therapy is necessary or desired, the rods are likely surgically removable early in therapy, as degradation of the compacted matrix is gradual. Overall, PLGA-based compacted long-acting buprenorphine rods provide a robust platform offering high drug loading, simplified processing, scalable manufacturing, and extended therapeutic duration.

CRediT authorship contribution statement

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

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Data availability

Data will be made available on request.

References

[1] Centers for Disease Control and Prevention, CDC reports nearly 24% decline in U.S. drug overdose deaths, 2025. Available from, https://www.cdc.gov/media/releases/2025/2025-cdc-reports-decline-in-us-drug-overdose-deaths.html.
[2] A. Barnett, et al., Tracing the affordances of long-acting injectable depot buprenorphine: a qualitative study of patients' experiences in Australia, Drug Alcohol Depend. 227 (2021) 108959.
[3] A.I. Leshner, M. Mancher, Medications for Opioid Use Disorder Save Lives, National Academies Press, Washington, DC, 2019.
[4] M. Soyka, Transition from full mu opioid agonists to buprenorphine in opioid-dependent patients: a critical review, Front. Pharmacol. 12 (2021) 718811.
[5] U.S. Food and Drug Administration, Information About Medication-assisted Treatment (MAT), Available from: https://www.fda.gov/drugs/information-drug-class/information-about-medication-assisted-treatment-mat, 2022.
[6] M. Chappuy, et al., Prolonged-release buprenorphine formulations: perspectives for clinical practice, Therapies 75 (5) (2021) 397–406.
[7] Clemans-Cope L, et al. Medicaid Prescriptions for Extended-Release Medications to Treat Opioid Use Disorder: State Trends from 2011 to 2018. Urban Institute; 2020.
[8] S. Poliwoda, et al., Buprenorphine and its formulations: a comprehensive review, Health Psychol. Res. 10 (3) (2022) 37517.
[9] Indivior Inc, Sublocade (Buprenorphine Extended-Release Injection) Prescribing Information, 2018.
[10] S.C. Sigmon, et al., An injection depot formulation of buprenorphine: extended bio-delivery and effects, Addiction 101 (3) (2006) 420–432.
[11] A. Otte, et al., Long-acting injectable buprenorphine PLGA microparticle formulation, Int. J. Pharm. 683 (2025) 126006.
[12] M. Albayaty, et al., Pharmacokinetic evaluation of once-weekly and once-monthly buprenorphine subcutaneous injection depots versus intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade, Adv. Ther. 34 (2) (2017) 560–575.
[13] Braeburn Inc, Brixadi (Buprenorphine Extended-Release Injection) Prescribing Information, 2023.
[14] H.A. Blair, Buprenorphine extended-release injection in the management of opioid use disorder: a profile of its use in the USA, Drugs Ther. Perspect. 40 (2) (2024) 61–71.
[15] Titan Pharmaceuticals, Probuphine (Buprenorphine) Implant Prescribing Information, 2016.
[16] J. White, et al., Open-label dose-finding trial of buprenorphine implants for treatment of heroin dependence, Drug Alcohol Depend. 103 (1) (2009) 37–43.
[17] W. Ling, S. Shoptaw, D. Goodman-Meza, Depot buprenorphine injection in the management of opioid use disorder, Subst. Abuse Rehabil. 10 (2019) 69–78.
[18] K. Park, et al., Injectable, long-acting PLGA formulations, J. Control. Release 304 (2019) 125–134.
[19] K. Park, et al., Potential roles of the glass transition temperature of PLGA microparticles in drug release kinetics, Mol. Pharm. 18 (2021) 18–32.
[20] A. Otte, B.K. Soh, K. Park, The impact of post-processing temperature on PLGA microparticle properties, Pharm. Res. 40 (11) (2023) 2677–2685.
[21] K. Park, PLGA-based long-acting injectable formulations, J. Control. Release 382 (2025) 113758.
[22] P. Maturavongsadit, et al., A new engineering process of biodegradable polymeric solid implants for ultra-long-acting drug delivery, Int. J. Pharm. 3 (2021) 100068.
[23] E. Mommers, et al., Nexplanon implant 3-year results, Am. J. Obstet. Gynecol. 207 (5) (2012) 388.e1–388.e6.
[24] N. Shore, Introducing Vantas, Eur. Urol. Suppl. 9 (8) (2010) 701–705.
[25] K. Saxena, N. Saxena, A biodegradable implant composition and process for long-term delivery of buprenorphine, WO2022145157, 2022.
[26] H. Patil, R.V. Tiwari, M.A. Repka, Hot-melt extrusion, AAPS PharmSciTech 17 (1) (2016) 20–42.
[27] J. Garner, et al., Impact of manufacturing conditions on PLGA depot release, J. Pharm. Sci. 107 (2018) 353–361.
[28] S.R. Kleppner, et al., In vitro and in vivo characterization of a buprenorphine delivery system, J. Pharm. Pharmacol. 58 (3) (2006) 295–302.
[29] United States Pharmacopeial Convention, USP Description and Solubility, 2012.
[30] L.R. Lawrence, J.K. Beddow, Powder segregation during die filling, Powder Technol. 2 (5) (1969) 253–259.
[31] J.C. Williams, Segregation of particulate materials, Powder Technol. 15 (2) (1976) 245–251.
[32] C. Bassand, et al., PLGA implants: impact of diameter, Eur. J. Pharm. Biopharm. 177 (2022) 50–60.
[33] A. Otte, H. Turasan, K. Park, Particle size effects in PLGA microparticles, Int. J. Pharm. 626 (2022) 122170.
[34] W. Chen, et al., Gefitinib-loaded PLGA microspheres, Mol. Pharm. 14 (2) (2017) 459–467.
[35] G. Acharya, et al., Drug release from homogeneous PLGA microstructures, J. Control. Release 146 (2) (2010) 201–206.
[36] D. Klose, et al., Porosity and size effects in PLGA microparticles, Int. J. Pharm. 314 (2) (2006) 198–206.
[37] A. Bauer, et al., Long-acting injectables: industry perspectives, Pharm. Res. 40 (7) (2023) 1601–1631.
[38] L. Smith, et al., Probuphine subdermal implants, P T. 42 (8) (2017) 505–508.
[39] A.K. Jones, et al., Population pharmacokinetics of monthly buprenorphine depot, Clin. Pharmacokinet. 60 (4) (2021) 527–540.
[40] Tice TR, Staas JK, Ferrell TM, Markland P. Injectable opioid partial agonist or opioid antagonist microparticle compositions. U.S. Patent US6495155; 2002.
[41] S. Koocheki, S.S. Madaeni, P. Niroomandi, Sustained release buprenorphine HCl formulation, Saudi Pharm. J. 19 (4) (2011) 255–262.
[42] Richey T, Thanoo BC. High drug-load buprenorphine microspheres. U.S. Patent US20160287834; 2016.
[43] H. Kamali, et al., PLGA-PEG-PLGA buprenorphine gel, Mater. Sci. Eng. C 96 (2019) 561–575.
[44] Yoon G, et al. Injectable long-acting naltrexone microparticle compositions. U.S. Patent US11013743B2; 2021.