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Parenteral sustained-release dosage forms of butorphanol for dogs

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Abstract

The objective of this study is to develop a sustained-release parenteral dosage form of butorphanol which can provide an analgesic effect over a 24-h period after subcutaneous administration. Four experimental 24-h butorphanol depot injections, two aqueous suspensions of butorphanol free base (5 and 10 mg/ml), and two oil suspensions of the tartrate salt (10 and 20 mg/ml) have been developed and evaluated in dogs. Each of the formulations was evaluated in a group of three animals; each dog received a 2 mg/kg subcutaneous dose of the depot injection. Butorphanol concentrations in plasma were monitored using HPLC for 72 h after dosing. The drug-plasma concentrations from the experimental depot injections were compared to those obtained from the reference solution injection Torbugesic-SA. It was found that butorphanol absorption from the Torbugesic-SA was significantly faster than that from the aqueous and oil suspensions. Also, the drug-plasma concentration was maintained within the desired therapeutic blood level (5–100 ng/ml) over a 24-h period for all four experimental butorphanol depot injections. Furthermore, the potential side effects of these experimental formulations are expected to be less because of the relatively lower peak concentrations (C_{max}) as compared to that of the solution injection Torbugesic-SA.

Keywords: Analgesic; Aqueous suspension; Butorphanol; Oil suspension; Sustained release; Subcutaneous

1. Introduction

Butorphanol, a synthetic morphinan derivative, was developed to minimize side effects associated

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with classical narcotic analgesics such as morphine and codeine (Heel et al., 1978). It has been classified as a potent analgesic with both agonist-antagonist effects. The analgesic potency of butorphanol is 3.5–7 times that of morphine, 30–40 times that of meperidine, 15–20 times that of pentazocine, and 1/40 that of naloxone (Swinyard, 1990). Butorphanol also has a strong antitussive effect, which is 100 times that of codeine (Booth, 1988).

Butorphanol is currently available for use in both humans and dogs (Heel et al., 1978; Sawyer and Rech, 1987; Hosgood, 1990). It is more suitable for the relief of acute, rather than chronic, pain. The usual dose is 1–4 mg of the tartrate salt given intramuscularly (IM), or 0.5–2 mg given intravenously (IV) every 3–4 h in humans (Swinyard, 1990). The current recommended dose for analgesia and sedation in dogs is 0.1–0.8 mg/kg IV, IM, or subcutaneously (SC) (Hosgood, 1990).

In dogs, butorphanol is absorbed and excreted rapidly, with a relatively short half-life ($t_{1/2}$ about 1.5 h) (Pfeffer et al., 1980). In addition, butorphanol induces a few moderate-to-marked adverse effects such as cardiopulmonary depression, cardiovascular depression, and panting when administered intravenously (Heel et al., 1978). With the goals of reducing frequency of drug administration, prolonging the therapeutic activity of the drug, and minimizing drug side effects, the concept of sustained-release parenteral dosage forms of butorphanol is here being formalized (Gibaldi and Perrier, 1982; Lordi, 1986; Silber et al., 1988).

A suspension is a widely used pharmaceutical dosage form which offers a potential use as a parenteral sustained-release system. Subcutaneous administration of a drug as an aqueous or oil suspension results in the formation of a depot at the injection site. The depot acts as a drug reservoir, slowly releasing the drug continuously at a rate dependent upon both the intrinsic aqueous solubility of the drug and the dissolution rate of the drug particles into the tissue fluid surrounding the drug particles in the subcutaneous tissue. In this study, aqueous suspensions of butorphanol free base and oil suspensions containing butorphanol tartrate are developed and evaluated in dogs. It is anticipated that the dissolved form of butorphanol in the aqueous suspension formulations can act as the loading dose which provides a fast onset after subcutaneous injection. The relatively water-insoluble free base of butorphanol in the aqueous suspension can function as the depot which dissolves over time and maintains the therapeutic activity. For an oil suspension, it is expected that the low solubility of butorphanol tartrate in the oil phase will result in a relatively slower onset; the suspended butorphanol tartrate will be gradually released into the aqueous medium surrounding the oil droplets via an interfacial dissolution process to produce the prolonged therapeutic activity.

The relationship between butorphanol blood level and therapeutic response (analgesic effects) in dogs is not clearly indicated in the literature (Heel et al., 1978; Hosgood, 1990). Pfeffer et al. (1980) reported that the serum butorphanol versus time data was in agreement with a linear, open one-compartment model with first-order drug absorption; the absorption rate-constant (K_a) is 7.3 h^{-1}, the elimination rate constant (K_e) is 0.424 h^{-1}, and the volume of distribution (V) is 8.42 l/kg after subcutaneous administration of 0.25 mg/kg butorphanol tartrate in dogs (Pfeffer et al., 1980). In our study, a therapeutic blood level of 5–100 ng/ml is proposed. This therapeutic range is the steady-state drug concentration (after six 4-h injections of 0.1–0.8 mg/kg) calculated using the pharmacokinetic parameters described above and an open one-compartment model. Therefore, an experimental formulation which can produce a drug-plasma level maintained within this desired range (5–100 ng/ml) for 24 h is considered to be a viable product.

2. Materials and methods

2.1. Materials

Butorphanol tartrate is a product of Abbott Laboratories (North Chicago, IL). Methylparaben, propylparaben, and Span 85 were purchased from Sigma (St. Louis, MO). Tween 80 was obtained from Aldrich (Milwaukee, WI). The soybean oil was purchased from Honeymead

Products (Mankato, MN). Potassium phosphate, monobasic, was purchased from Fisher Scientific (Fair Lawn, NJ). Sodium hydroxide 1 N and sulfuric acid 1 N were obtained from VWR Scientific (West Chester, PA).

2.2. Experimental methods

2.2.1. Preparation of oil suspensions

Two oil suspensions were prepared with the formulation listed in Table 1. To prepare an oil suspension, a predetermined amount of spray-dried butorphanol tartrate (2–10 μm) was placed in a beaker and a predetermined amount of a suspending agent (Span 85) was added and mixed with the drug until a smooth paste was formed. Oil was subsequently added in small portions with continuous stirring until the required volume was made. The final product was mixed using a Silverson® L-4RT high-shear mixer (Silverson Machines, East Longmeadow, MA) for 5 min at 5000 rpm and stored at room temperature for further evaluation.

2.2.2. Preparation of aqueous suspensions

In the preparation of the aqueous suspensions, butorphanol tartrate was used as the starting material and the free base was produced in-situ by neutralizing the salt with a base solution. Two aqueous suspensions (Table 2) were prepared and evaluated. The preparation procedures are described below.

2.2.2.1. 5 mg/ml Aqueous suspension. Forty milligrams of methylparaben, 4 mg propylparaben, and 1 g Tween 80 were dissolved in 140 g phosphate buffer by heating the mixture to ~55°C.

Table 1
Formulation of 10 and 20 mg/ml oil suspension

Ingredient	Amount in 10 mg/ml formulation	Amount in 20 mg/ml formulation
Butorphanol tartrate	1.0 g	2.0 g
Span 85	1.0 g	1.0 g
Soybean oil	q.s. to 100 ml	q.s. to 100 ml

Table 2
Formulation of 5 mg/ml aqueous suspension

Ingredient	Amount
Butorphanol tartrate	1.0 g
Tween 80	1.0 g
Phosphate buffer (0.2 M)	140.0 g
Methylparaben	40.0 mg
Propylparaben	4.0 mg
1 N NaOH	24.0 g
Water for injection	q.s. to 200 ml

One gram of butorphanol tartrate was dissolved in the solution. Sodium hydroxide 1 N was then added dropwise into the solution to produce butorphanol free base under agitation using the Silverson® L-4RT high-shear mixer at 7000 rpm. Water for injection was added to make the final volume of 200 ml. The pH of the suspension was 6.25. The resulting suspension was passed through the Microfluidizer 110Y (Microfluidics, Newton, MA) for 10 cycles with the 75-μm interaction chamber and 200-μm back-pressure module at 12000 psi. The drug particle size was estimated by optical microscopy to be in the range of 5–10 μm.

2.2.2.2. 10 mg/ml Aqueous suspension (Table 3). The preparation procedures for this formulation are similar to those for the 5 mg/ml suspension. One gram of Tween 80 was dissolved in 120 g citrate buffer by heating the mixture to ~55°C. One gram of butorphanol tartrate was then dissolved in the solution. Sodium hydroxide 1 N was added dropwise into the solution to produce butorphanol free base under agitation using the Silverson L-4RT high-shear mixer at 7000 rpm. Water for injection was added to make the final

Table 3
Formulation of 10 mg/ml aqueous suspension

Ingredient	Amount
Butorphanol tartrate	2.0 g
Tween 80	1.0 g
Citrate buffer (0.2 M)	120.0 g
1 N NaOH	61.0 g
0.1 N NaOH	5.0 g
Water for injection	q.s. to 200 ml

volume of 200 ml. The pH of the suspension was 7.00 and the particle size was estimated by optical microscopy to be between 30 and 40 μm.

2.2.3. Analysis of butorphanol content in formulations

2.2.3.1. Aqueous suspension. The drug content of butorphanol/aqueous suspensions was analyzed by high performance liquid chromatography (HPLC). One milliliter of the aqueous suspension was pipetted into a 100 ml volumetric flask. Then 10 ml of 1 N sulfuric acid were added to dissolve the drug. The volume was then made up to 100 ml with water and directly injected onto the HPLC. The drug content in the solution phase was determined by filtering 3 ml of the suspension through a 0.22 μm filter. The filtrate was then directly injected onto the HPLC.

The HPLC system consisted of a Shimadzu® Model SIL-9A autoinjector, a Shimadzu® Model SPD-6A UV spectrophotometer, a Shimadzu® Model LC-6A liquid chromatograph, and a Shimadzu® Model CR501 integrator. The stationary phase was a μBondapak™ Phenyl column (3.9 × 300 mm, Waters, USA). The mobile phase was prepared by mixing 1 l of 0.05 M ammonium acetate and 335 ml of acetonitrile, with a pH adjustment to 4.1 using glacial acetic acid. The chromatogram was monitored by UV detection at the maximum wavelength of 280 nm, with a sensitivity setting of 0.08 AUFS. The injection volume was 100 μl and the flow rate was 2 ml/min. The resolution factor was larger than two and the limit of detection was 5 μg/ml. The assay was linear over the concentration range 50–2012 μg/ml, with a mean percent deviation $< 7.0\%$ for the analysis of triplicate standards at six separate concentrations.

2.2.3.2. Oil suspension. The drug content of butorphanol tartrate/oil suspension was analyzed by HPLC. Subsequently 1 ml of the oil suspension was pipetted and placed in a centrifuge tube. Then, 10 ml of 1 N sulfuric acid were added. The tubes were shaken using a Burell wrist-action shaker for a period of 15 min and then centrifuged for 5 min at 3000 rpm. The aqueous phase was separated from the oil phase and further diluted before being injected into the column. The amount of drug in the oil solution phase was determined by filtering 3 ml of the oil suspension through a 0.22 μm filter. Then 1 ml of this filtrate was pipetted into a centrifuge tube and 10 ml of 1 N sulfuric acid were added to the tube, which was subsequently shaken and centrifuged as described above. The aqueous solution was sampled and injected directly onto the HPLC.

2.2.4. In-vitro drug release

A predetermined amount of aqueous or oil suspension was transferred, in duplicate, into dialysis tubing (Spectra®/Por2, MWCO 12000–14000), which was placed in the dialyzate, 100 ml of 0.1 M phosphate buffer (pH 7.4). Agitation was achieved using a magnetic stirrer at a speed of 600 rpm. At a predetermined sampling-time interval, 1 ml of the dialyzate was withdrawn for drug-content assay using the HPLC method described in the previous section (analysis of butorphanol content in formulations). The drug-release study was maintained under sink conditions by discarding and replacing the dialyzate with fresh medium at each sampling-time point. The drug-release data reported in this study are an average of duplicate samples.

The dialysis membrane was first tested to check whether it was a rate-limiting barrier to drug release. When a 5 mg/ml solution of butorphanol tartrate was placed into the dialysis tubing and the tubing was immersed in 500 ml of dissolution medium, 87.6% of the drug was released in 1 h; complete drug release was accomplished within 3 h. The results confirm that the membrane did not act as a rate-limiting barrier for the test formulations.

2.2.5. In-vivo evaluation of formulations (in dogs)

2.2.5.1. Animal study design. Fifteen beagle dogs were obtained from the established Abbott Drug Analysis Colony. The dogs were randomly assigned to one of five groups of three, each group represented by formulations A–E (Table 4).

The dogs received a 2 mg/kg subcutaneous dose of either one of the experimental suspension for-

Table 4
Formulations evaluated in dogs

Formulation	Concentration (mg/ml)	Description
A	5	Aqueous suspension
B	10	Aqueous suspension
C	10	Oil suspension
D	20	Oil suspension
E	2	Torbugesic-SA solution

mulations or the reference solution injection. Heparinized blood samples were obtained from the jugular vein of each dog prior to dosing and 0.25, 0.5, 1, 2, 4, 6, 9, 12, 15, 24, 48, and 72 h after dosing. The plasma was separated from the red cells by centrifugation (2500 rpm × 10 min, 4°C) and frozen (− 20°C) for subsequent analysis.

2.2.5.2. Drug analysis for animal study. Butorphanol and the internal standard (Abbott-81631) were separated from the plasma matrix using liquid–liquid extraction with chloroform under alkaline conditions. Plasma (0.5 ml) was mixed with 0.1 ml internal standard, 1.0 ml 1 N NaOH, and 7 ml chloroform. The samples were vortexed for 20 s, followed by centrifugation. The upper aqueous layer was aspirated to waste. The organic layer was transferred into a conical centrifuge tube and evaporated to dryness with a gentle stream of dry air over low heat (∼ 35°C). The samples were reconstituted in 0.2 ml of acetonitrile:water (3:7, by volume). Butorphanol plasma standards were analyzed simultaneously with the samples.

Butorphanol and the internal standard were separated from the co-extracted plasma contaminants on a 25 cm × 4.6 mm ODS-AQ (YMC) column using an acetonitrile: methanol:buffer mobile phase (16:10:74, by volume) at a flow rate of 1.0 ml/min. The mobile-phase buffer was comprised of 0.05 M potassium phosphate with 0.01 M tetramethylammonium perchlorate adjusted to pH 6.0 prior to being combined with the organic fractions. Electrochemical detection in the oxidative mode (DET1 = + 0.4 V, DET2 = + 0.85 V) was used for quantitation of the analytes.

The plasma-drug concentration of each sample was calculated by least-squares linear regression analysis of the peak-area ratio (parent/internal standard) of the spiked plasma standards versus concentration. The limit of detection was 1 ng/ml and the assay was linear over the concentration range 1–533 ng/ml, with a mean percent deviation < 6.5% for the analysis of triplicate standards at seven separate concentrations. The maximum plasma concentrations (C_{max}) and the times to reach the maximum plasma concentrations (T_{max}) were read directly from the observed plasma concentration–time data. The area under the plasma concentration–time curve was calculated using the linear trapezoidal rule over the single 72-h dosing interval ($AUC_{0\text{-}72}$).

3. Results and discussion

3.1. Butorphanol content in suspensions

The drug content of each experimental formulation was determined prior to the animal study (Table 5). The actual drug content (butorphanol tartrate) is 5.36 and 9.60 mg/ml for the 5 and 10 mg/ml aqueous suspensions, respectively, and 8.90 and 18.00 mg/ml for the 10 and 20 mg/ml oil suspensions, respectively. The high percent (60.2%) of drug in the solution phase of the aqueous suspension with a lower pH (6.25) is attributed to the high solubility of the drug (pK_a 8.6) at this low pH. In oil suspensions, the drug in the oil phase was found to be less than 0.5%. Most of the drug in the oil suspension remained as the undissolved tartrate salt dispersed in the oil.

3.2. In-vitro drug release

The in-vitro drug-release profiles for selected formulations are shown below. Fig. 1 shows that the drug-release profiles for the 10 and 20 mg/ml oil suspensions are comparable. Total drug release is over 80% after 48 h. The data also indicate that the increase in the percent of oil does not result in a slower drug release in spite of a greater amount of oil surrounding the drug particles. The drug-re-

Table 5
Drug contents of four experimental formulations

Formulation	Actual drug content (mg/ml)	Drug in solution phase (%)
Aqueous suspension, pH 6.25 (5 mg/ml)[a]	5.36	60.2
Aqueous suspension, pH 7.00 (10 mg/ml)[a]	9.60	5.0
Oil suspension of butorphanol tartrate (10 mg/ml)[a]	8.90	<0.5
Oil suspension of butorphanol tartrate (20 mg/ml)[a]	18.00	<0.5

[a] Target dose of butorphanol tartrate.

lease profiles of butorphanol free base from aqueous suspensions with two different pHs and drug-particle sizes are shown in Fig. 2. The total cumulative drug release from these two aqueous formulations are both close to 100% after 48 h. However, drug release in the first 24 h is almost close to completion for the 5 mg/ml suspension (pH 6.25) as compared to that (~ 58%) for the 10 mg/ml suspension (pH 7.00). The faster release rate for the low-pH suspensions is attributed to the higher solubility (60.2% dissolved) of the drug at this low pH and the smaller drug-particle size in the suspension. Also, a higher burst-release is shown by this formulation (pH 6.25) because of the higher percentage of drug in the solution phase.

The in-vitro data indicate that salt forms in a suspension play an important role in determining drug release. In the 10 mg/ml aqueous suspension (pH 7.00), the majority (~ 95%) of butorphanol is a free base which has a relatively lower intrinsic solubility in the dissolution medium as compared to that of tartrate salt. On the other hand, only ~ 40% of the butorphanol in the 5 mg/ml aqueous suspension (pH 6.25) remains as free base and 60% is present as dissolved tartrate salt. As mentioned above, the aqueous suspension with the higher percentage of dissolved tartrate salt released faster. Therefore, the amount of dissolved drug in the aqueous phase of a suspension provides

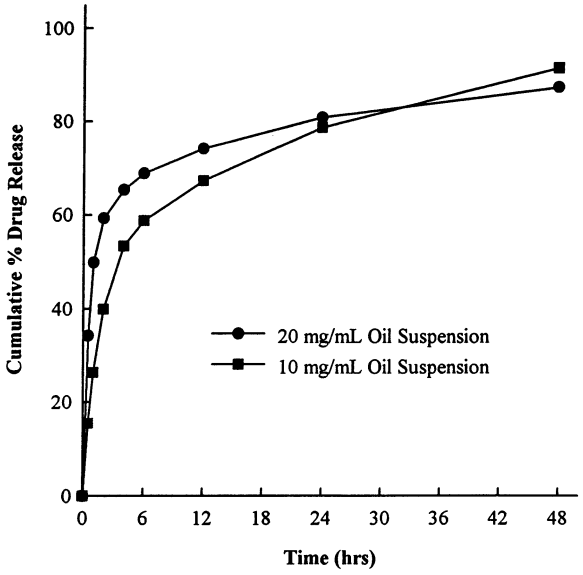

Fig. 1. In-vitro release of butorphanol from oil suspensions ($n = 2$). Circles, 20 mg/ml oil suspension; squares, 10 mg/ml oil suspension.

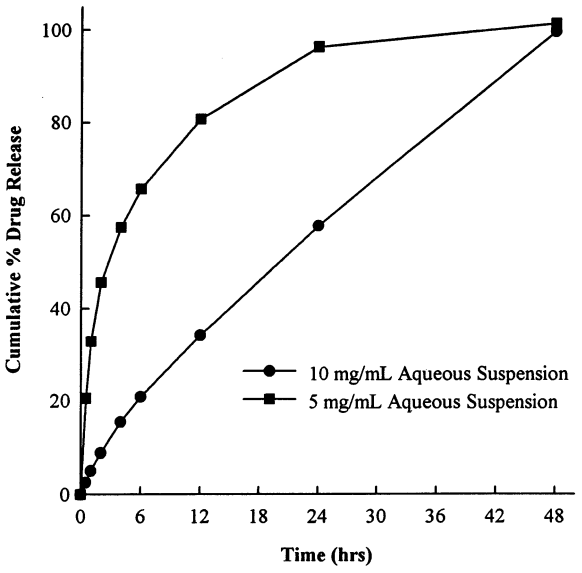

Fig. 2. In-vitro release of butorphanol from aqueous suspensions ($n = 2$). Circles, 10 mg/ml aqueous suspension; squares, 5 mg/ml aqueous suspension.

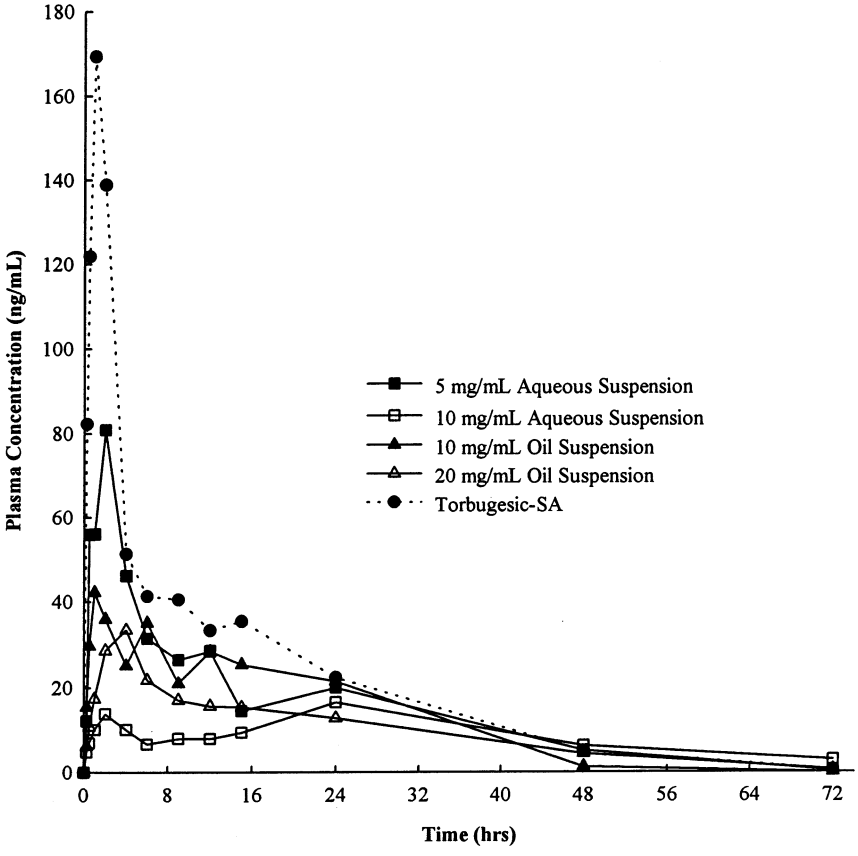

Fig. 3. Mean plasma concentrations of butorphanol after a 2 mg/kg subcutaneous dose of various formulations in dog ($n = 3$). Filled squares, 5 mg/ml aqueous suspension; open squares, 10 mg/ml aqueous suspension; filled triangles, 10 mg/ml oil suspension; open triangles, 10 mg/ml oil suspension; filled circles, Torbugesic-SA.

the loading dose of the drug. In addition, we also compared the drug release in the suspensions prepared by different vehicles (i.e. oil vs aqueous). Drug release in the first 24 h is about 80% for the 10 mg/ml oil suspension (Fig. 1) as compared to 96% for the 5 mg/ml aqueous suspension (Fig. 2). Most of the drug ($>99\%$) remains in the oil suspension as tartrate salt surrounded by the oil medium. The main mechanism for drug dissolving into the aqueous medium is by the dissolution of the tartrate salt particles at the oil/aqueous interface. However, the 5 mg/ml aqueous suspension shows a relatively faster drug release with only 60% of the drug in the tartrate salt form. It is clear that oil serves as a better barrier than water for controlling drug release. These results also suggest that vehicle type (oil vs aqueous) could be another factor affecting drug release. It is anticipated that these two factors, salt form and vehicle type, would have similar effects on in-vivo drug release.

3.3. In-vivo evaluations of formulations

Four experimental sustained-release suspensions, two aqueous suspensions, and two oil suspensions were administered to four different groups of three beagle dogs. Each formulation was evaluated using a 2 mg/kg subcutaneous dose. The drug-plasma concentrations were compared to those obtained from an equal dose of the solution injection, Torbugesic-SA. The mean butorphanol plasma concentrations over time are given (mean $\pm$ S.D., $n = 3$) in Table 6. Plots of the

Table 6
Plasma concentration of butorphanol after 2 mg/kg subcutaneous administration of various formulations evaluated

		Plasma concentration (ng/ml)											
		0.25 h	0.5 h	1 h	2 h	4 h	6 h	9 h	12 h	15 h	24 h	48 h	72 h
5 mg/ml aqueous suspension	Mean (S.D.)[a]	12.2 (10.9)	55.9 (56.8)	56.0 (53.4)	80.9 (68.4)	46.1 (22.0)	31.4 (8.9)	26.4 (11.9)	28.5 (17.0)	14.5 (2.9)	20.0 (13.8)	5.2 (2.2)	0.4 (0.7)
10 mg/ml aqueous suspension	Mean (S.D.)[a]	4.7 (1.1)	7.0 (3.2)	10.1 (2.2)	13.8 (2.2)	10.1 (2.4)	6.7 (0.9)	8.0 (5.0)	8.0 (3.0)	9.4 (5.0)	16.5 (5.6)	6.3 (2.7)	2.9 (3.2)
10 mg/ml oil suspension	Mean (S.D.)[a]	15.5 (5.3)	29.7 (12.3)	42.2 (5.9)	35.9 (12.5)	25.1 (7.1)	35.0 (9.9)	21.0 (6.0)	28.5 (13.7)	25.4 (9.7)	21.5 (7.8)	1.3 (1.5)	N/A[b]
20 mg/ml oil suspension	Mean (S.D.)[a]	6.2 (3.5)	10.8 (5.2)	17.4 (10.6)	28.6 (11.4)	33.3 (12.9)	21.8 (9.4)	17.1 (5.1)	15.7 (5.5)	15.4 (0.3)	12.8 (1.1)	4.4 (4.1)	0.7 (1.1)
2 mg/ml Torbugesic-SA	Mean (S.D.)[a]	82.2 (17.3)	121.9 (21.2)	169.3 (66.7)	138.9 (43.5)	51.3 (18.8)	41.2 (3.9)	40.5 (15.5)	33.3 (14.5)	35.4 (16.7)	22.3 (12.8)	5.0 (2.4)	0.6 (0.5)

[a] Mean ± standard deviation, $n = 3$.
[b] Not available.

Table 7
Pharmacokinetic parameters after a 2 mg/kg subcutaneous administration of various formulations evaluated

		C_{max} (ng/ml)	T_{max} (h)	AUC_{0-72} (ng · h/ml)
5 mg/ml Aqueous suspension	Mean (S.D.)[a]	80.9 (68.4)	2.0	1068.9 (401.0)
10 mg/ml Aqueous suspension	Mean (S.D.)[a]	13.8 (2.2)	2.0	632.0 (175.6)
10 mg/ml Oil suspension	Mean (S.D.)[a]	42.2 (5.9)	1.0	923.8 (232.9)
20 mg/ml Oil suspension	Mean (S.D.)[a]	33.3 (12.9)	4.0	698.1 (49.2)
2 mg/ml Torbugesic-SA	Mean (S.D.)[a]	169.3 (66.7)	1.0	1537.5 (489.3)

[a] Mean ± standard deviation, $n = 3$.

butorphanol-plasma concentrations versus time for the five formulations are shown in Fig. 3. The pharmacokinetic parameters: C_{max}, T_{max}, and AUC_{0-72} are given (mean ± S.D., $n = 3$) in Table 7.

Fig. 3 shows that butorphanol was rapidly absorbed from Torbugesic-SA, with the peak concentration (169.3 ± 66.7 ng/ml) recorded 1 h after dosing, followed by a rapid decline in drug concentration. This high peak blood level is likely to cause adverse effects such as cardio-pulmonary depression, cardiovascular depression, and panting, which were usually observed after the I.V. administration of butorphanol (Hosgood, 1990).

On the other hand, a slower, but more variable, absorption was noted following subcutaneous administration of the aqueous suspensions, yielding the peak concentrations at 2.0 h after dosing with the 5 and 10 mg/ml formulations (Fig. 3 and Table 7). The T_{max} values for the 10 and 20 mg/ml oil suspensions are 1 and 4 h, respectively. These results indicate that the onset of the 10 mg/ml oil suspension was probably relatively faster than those of the other three formulations. It is known that, in this oil suspension, very small drug particles of butorphanol tartrate (2–10 μm) are dispersed in the continuous oil phase. The faster absorption may be attributed to the relatively quick dissolution of these small drug particles at the oil/aqueous interface. The relatively large surface area of the smaller particles for dissolution may also enhance drug absorption.

Lower peak concentrations were noted (Table 7) for all the experimental sustained-release formulations, with C_{max} values averaging 42.2 ± 5.9 and 33.3 ± 12.9 ng/ml for the 10 and 20 mg/ml oil suspensions, respectively, and 80.9 ± 68.4 and 13.8 ± 2.2 ng/ml for the 5 and 10 mg/ml aqueous suspensions, respectively (mean ± S.D., $n = 3$). These results suggest that the potential side effects of these experimental formulations are expected to be less because of their relatively lower C_{max} as compared to that of the reference solution injection. The moderate fluctuation of the butorphanol-plasma concentration versus time profiles (Fig. 3) may indicate variable absorption from the suspension formulations or an apparent enterohepatic recycling of the parent drug.

The results from the animal study indicate that the four evaluated experimental formulations produced a sustained-release profile of butorphanol (Fig. 3 and Table 6). Also, the drug-plasma concentration was maintained within the desired blood level (5–100 ng/ml) over a 24-h period for all experimental formulations.

From the results in Table 6 and Fig. 3, it was found that the extent of drug absorption is faster in the 5 mg/ml aqueous suspension than in the 10 mg/ml aqueous suspension. This observation corresponds to the results from the in-vitro drug release study which shows the drug release is faster in the 5 mg/ml aqueous suspension compared to that in 10 mg/ml aqueous suspension. It can also be seen in Table 7 that the highest C_{max} and AUC_{0-72} were associated with the 5 mg/ml aqueous suspension. Again, this is probably attributable to the higher percentage ($> 60\%$) of dissolved tartrate salt in the 5 mg/ml suspension compared to less than 5% of that in the 10 mg/ml suspension. Moreover, in the previous in-vitro drug release study, it was found that the oil phase is a better barrier for controlling drug release than is the aqueous system when the drug releases of the 5 mg/ml aqueous suspension and 10 mg/ml oil

suspension are compared. This finding is again supported by the data collected in the in-vivo study here. As it is given in Table 7, the extent of drug absorption in the 5 mg/ml aqueous suspension (C_{max}80.9 ng/ml and $AUC_{0\text{-}72}$ 1068.9 ng · h/ml) is faster than in the 10 mg/ml oil suspension (C_{max}42.2 ng/ml and $AUC_{0\text{-}72}$ 923.8 ng · h/ml). These results suggest that the data in the in-vitro drug release can be somewhat correlated to the results of the in-vivo study. A comparison between the drug-plasma concentration profiles and pharmacokinetics parameters of the two oil suspensions indicates that an increase in the amount of oil in the suspensions yielded a greater extent of drug absorption. This can be attributed to the large injection volume, which allows more spreading of the formulation and an increase in surface area for drug dissolution. It is also interesting to find that drug absorption in the 10 mg/ml oil suspension is faster than in the 10 mg/ml aqueous suspension. In the oil suspension, most of the drug ($>99\%$) is spray-dried tartrate salt (2–10 μm) dispersed in the oil phase. On the other hand, the majority of butorphanol in the 10 mg/ml aqueous suspension is a free base with particle sizes ranging from 30–40 μm. It is obvious that both the particle sizes and salt forms make a significant impact on drug absorption.

Finally, in comparison with the $AUC_{0\text{-}72}$ of Torbugesic-SA, the relatively lower $AUC_{0\text{-}72}$ value for all experimental formulations indicates that a substantial amount of drug may still remain at the site of injection 72 h after administration and that the release of drug may continue for a prolonged period of time even at a very low concentration. Therefore, the maintenance dose of these experimental formulations can be further reduced.

4. Conclusions

Four experimental butorphanol parenteral sustained-release dosage forms, two aqueous suspensions of butorphanol free base, and two oil suspensions of the tartrate salt have been developed and evaluated in dogs. The in-vivo results indicate that these four experimental depot injections all showed a sustained drug-release profile, with the plasma-drug concentration maintained within the desirable therapeutic range of 5–100 ng/ml over a 24-h period.

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