

Formulation Selection and Pharmacokinetic Comparison of Fentanyl Buccal Soluble Film with Oral Transmucosal Fentanyl Citrate

A Randomized, Open-Label, Single-Dose, Crossover Study

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Abstract

Background and Objectives: BioErodible MucoAdhesive (BEMA[®]) is a new transmucosal drug delivery system designed to improve and ease the administration of drugs by this route. The first product that uses this novel delivery system contains fentanyl and is intended for the treatment of breakthrough pain in opioid-tolerant patients with cancer. The generic name is fentanyl buccal soluble film (FBSF). The objectives of this study were to compare the pharmacokinetic profile of FBSF formulations at three different pHs (pH 6, pH 7.25 and pH 8.5) and to understand the differences in the pharmacokinetics of fentanyl from FBSF compared with that of oral transmucosal fentanyl citrate (OTFC).

Methods: This was a randomized, open-label, single-dose, four-period, Latin-square crossover study consisting of a 9-day inpatient treatment period. The study was conducted at a phase 1 clinical research unit in Austin, TX, USA. Twelve healthy subjects were enrolled, nine males and three females, between the ages of 21 and 44 years. Each subject received four 800 µg doses of fentanyl: single doses of the three FBSF formulations (pH 6, pH 7.25 and pH 8.5) and OTFC, with concurrent naltrexone. Plasma fentanyl concentrations were measured over a 48-hour period after each study dose. Pharmacokinetic parameters were calculated and compared.

Results: Peak plasma fentanyl concentrations (C_{\max}) and overall fentanyl systemic exposure (area under the plasma concentration-time curve from time zero extrapolated to infinity [AUC_{∞}]) for each of the three FBSF formulations were greater than for OTFC. The pH 7.25 FBSF formulation provided the earliest time to reach C_{\max} (t_{\max}), the highest C_{\max} value and the greatest AUC_{∞} value. Compared with OTFC, peak plasma fentanyl

concentrations with pH 7.25 FBSF were significantly higher (mean C_{\max} 1.67 vs 1.03 ng/mL; $p < 0.05$). Overall exposure was also greater with pH 7.25 FBSF than with OTFC (mean AUC_{∞} 14.5 vs 10.3 ng • h/mL).

Conclusions: All three FBSF formulations produced greater peak plasma concentrations and overall exposure to fentanyl than OTFC. In particular, the pH 7.25 FBSF formulation showed the most favourable pharmacokinetic profile of the three FBSF formulations. In comparison with OTFC, the pH 7.25 FBSF formulation produced the fastest and most efficient fentanyl delivery and was selected for further clinical development.

Background

Fentanyl buccal soluble film (FBSF) is an oral transmucosal form of fentanyl citrate, a potent opioid analgesic, intended for application to the buccal mucosa. The BioErodible MucoAdhesive (BEMA[®]) delivery technology consists of two different layers made of water-soluble polymeric films, one bioadhesive layer and one inactive layer. The bioadhesive layer contains fentanyl citrate and immediately adheres upon contact with the moist buccal mucosa, and the inactive layer isolates the bioadhesive layer from the buccal cavity, minimizing the amount of fentanyl that is swallowed and facilitating delivery directly to the buccal mucosa.^[1] FBSF starts to dissolve in minutes and is completely dissolved within 15–30 minutes after application, without patient effort. The available dosage strengths range from 200 to 1200 µg, and the amount of fentanyl delivered transmucosally is proportional to the film surface area.

FBSF is being investigated for the management of breakthrough pain in opioid-tolerant patients with cancer. Patients with cancer often experience persistent around-the-clock pain that is typically controlled through the use of extended-release analgesics, most commonly opioids, taken according to a regular schedule. Patients with cancer can also experience breakthrough pain episodes, i.e. transient exacerbations of pain occurring even though persistent pain is relatively stable and adequately controlled.^[2] These breakthrough pain episodes can be sudden and very intense. Optimal management of breakthrough pain requires the use of

potent, fast-acting analgesics. Orally administered medications such as morphine, hydro-morphine and oxycodone in short-acting tablets, capsules or liquids are most commonly used for the treatment of breakthrough pain; however, these agents may be subject to delayed onset due to the time required to reach the absorption sites in the intestine, the slow gastrointestinal motility occurring in patients taking opioid therapy, and the limited bioavailability that results from first-pass metabolism.^[3] Additionally, oral delivery of analgesics can be problematic for patients who have difficulty swallowing, are nauseated or have other gastrointestinal conditions.

Because of these limitations, the need for alternative dosage forms that provide acute relief of breakthrough pain led to the development of products based on transmucosal delivery of fentanyl. However, current transmucosal technologies still have limitations with respect to overall bioavailability, consistency of dose delivery, lack of bioequivalence when titrating, or site administration tolerability.^[4–10] In addition, active patient participation throughout the administration process, which may take upwards of 25 minutes, is required for proper administration to achieve the most efficient delivery of fentanyl with these products.^[4]

Optimal delivery of fentanyl through the buccal mucosa requires maximization of both drug dissolution in saliva and drug absorption through the oral mucosa. FBSF was designed to reduce continuous patient participation in dosing, produce more consistent pharmacokinetics and, therefore, provide a more reliable analgesic

effect. As the dissolution and buccal absorption of fentanyl are both pH-dependent processes,^[11,12] one objective of this study (Study FEN-107) was to evaluate how the pH of FBSF affects drug delivery. This was the first study conducted with this manufacturing process for FBSF. Fentanyl is more soluble below pH 6, but a greater percentage of the dose is present in the ionized form. The formulations tested varied in pH around the acid dissociation constant (pKa) of fentanyl (7) in an attempt to assess gross differences in pharmacokinetics and select the best formulation to advance into patient trials.

Oral transmucosal fentanyl citrate (OTFC) was included as an internal control to avoid the error introduced by comparison of results across studies. A second objective of the study was to understand the differences in the pharmacokinetics of fentanyl from the buccal soluble film delivery system compared with OTFC.

Subjects and Methods

Subjects

The sample size of 12 subjects chosen for this study was based on conventional pharmacokinetic study designs, not a formal power calculation. Eligible subjects were males or females aged 18–45 years with a bodyweight of 50–100 kg and within 15% of ideal bodyweight based on Metropolitan Life tables for height and weight.^[13] Subjects were required to be free of any significant clinical abnormalities on the basis of medical history, physical examination, ECG and screening laboratory tests. Subjects were required not to consume alcohol (ethanol) or foods or beverages containing caffeine/xanthine or grapefruit within 48 hours of the first dose of study medication and for the duration of the study. They were also required not to have used tobacco or nicotine products within 30 days prior to the first dose of study medication. In addition, subjects were excluded from the study if they had any significant medical condition either currently or in their past history, including glaucoma and seizure disorders, had participated in any investigational drug study within the past 30 days,

had a positive drug screen, or had taken any concomitant medication (including prescription, nonprescription or nutritional supplements) other than oral contraceptives or paracetamol (acetaminophen) within 72 hours prior to the first dose of study medication. Pre-menopausal women who were not using a medically accepted method of contraception or had a positive urine β -human chorionic gonadotropin test were excluded. Subjects with a history of allergic reaction or significant intolerance to opioids were also excluded from this study.

Subjects were required to sign an informed consent form, which had been reviewed and approved by a regional Institutional Review Board (IntegReview Ethical Board, Austin, TX, USA). This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the Code of Federal Regulations, Title 21, Part 50.

Study Design

The study was a randomized, open-label, single-dose, four-period study using a Latin-square crossover design conducted in a phase 1 clinical research unit (CEDRA Clinical Research, Austin, TX, USA). The study consisted of a screening visit within 21 days before study drug administration, after which subjects were admitted to the phase 1 unit for a 9-day inpatient treatment period and received the study drug on days 1, 3, 5 and 7. Subjects received naltrexone (which does not alter the pharmacokinetics of fentanyl) at 12 hours and 0.5 hours pre-dose and 12 hours post-dose to block the respiratory depressive effects of fentanyl. Eligible subjects were given unique 3-digit subject numbers and assigned to one of the four different treatment sequences according to the Latin-square design. Each subject received four 800 μ g doses of fentanyl: one dose each of three FBSF formulations (pH 6, pH 7.25 and pH 8.5) [OnsolisTM, Meda Pharmaceuticals Inc., Somerset, NJ, USA] and a single dose of OTFC (Actiq[®], Cephalon, Inc., Salt Lake City, UT, USA). All study drug doses were administered by site personnel. FBSF was placed on the buccal mucosa inside the jaw approximately

1 inch (2.5 cm) from the edge of the mouth and held in place for a few seconds until the film adhered. Each subject's mouth was checked at intervals over the first hour after application. After adherence, the film remained on the buccal mucosa until it dissolved completely (approximately 15–30 minutes), which required no active effort by the subject. OTFC lozenges were administered according to the prescribing information.^[4]

Venous blood samples (7 mL) were collected in K₃-ethylenediamine tetraacetic acid (K₃-EDTA) Vacutainer[®] tubes just prior to each fentanyl dose and at 5, 7.5, 10, 15, 20, 25, 30, 45 and 60 minutes and at 2, 3, 4, 8, 12, 16, 20, 24 and 48 hours post-dose for measurement of plasma fentanyl concentrations. Subjects were discharged from the phase 1 unit on day 9 following the last 48-hour pharmacokinetic blood sample collection.

Bioanalytical Methods

Human plasma containing fentanyl and the internal standard, fentanyl-D5, were extracted into ethyl acetate/cyclohexane in the presence of base. Following centrifugation, the organic layer was transferred and evaporated to dryness. An aliquot of the reconstituted extract was injected onto a Sciex API 3000[™] liquid chromatography-tandem mass spectrometer (LC-MS/MS) equipped with a high-performance liquid chromatography (HPLC) column. Peak areas of the *m/z* 337 → 188 product ion of fentanyl were measured against the *m/z* 342 → 188 product ion of the internal standard. Quantitation was performed using weighted ($1/x^2$) linear least-squares regression analyses generated from fortified plasma calibration standards prepared immediately prior to each run.

Calibration standards prepared at seven different fentanyl concentrations were assayed on three separate days and the lower limit of quantification (LLQ) was established at 0.0250 ng/mL. The assay procedure was found to be linear over the range of 0.0250–5.00 ng/mL. The weighting of $1/x^2$ was selected based on power for weights calculations. Weighted linear least-squares regression analyses gave a mean correlation coefficient of 0.9992 over the three validation days.

Precision and accuracy were evaluated by treating the peak areas of the calibration standards as unknowns and entering them into the derived equation for the least-squares regression line to obtain 'amount found' values. The coefficient of variation (CV) ranged from 1.3% to 5.4%. The absolute deviation of the mean from the theoretical concentration ranged from 0.00% to 2.3%.

Precision and accuracy at the LLQ were verified by analysing at least two samples at the lowest standard concentration (0.0250 ng/mL) on each day of validation. The interday CV was 8.7% and the interday absolute deviation was 1.1%. The intraday precision and accuracy at the LLQ were verified by analysing six samples at the lowest standard concentration during one day of validation. The intraday CV was 4.8% and the intraday absolute deviation was 5.6%.

At least two samples from each quality control (QC) pool (high, medium and low) were processed on each day of validation. The interday CV for the three QC pools ranged from 2.7% to 6.7%. The interday absolute deviation of the mean from theoretical concentration ranged from 1.8% to 3.4%. On one day of validation, six samples from each QC pool (very high, high, medium and low) were processed. The intraday CV for the four QC pools ranged from 1.3% to 3.7%. The intraday absolute deviation ranged from 0.40% to 5.7%.

Data Analysis

Data from all subjects were included in the pharmacokinetic analyses and were analysed by noncompartmental methods using WinNonlin[®] version 4.0 (Pharsight Corporation, Mountain View, CA, USA). Pharmacokinetic calculations were based on actual sampling times. Concentration-time data that were below the limit of quantification (BLQ) [<0.0250 ng/mL] were treated as zero from time zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as missing. Unrounded concentration data were used for all pharmacokinetic and statistical analyses.

Maximum drug concentration in plasma (C_{\max}), first quantifiable plasma concentration (C_{first}), time to reach C_{first} (t_{first}) and time to reach C_{\max} (t_{\max}) were determined from individual subject concentration-time profiles. Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last}) was calculated using the linear trapezoidal rule. AUC from time zero to infinity (AUC_{∞}) was calculated as $AUC_{\text{last}} + C_{\text{last}}/\lambda$, where C_{last} is the last quantifiable plasma concentration and λ is the observed terminal elimination rate constant. Calculation of λ was performed using unweighted linear regression analysis on at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal slope. Terminal elimination half-life ($t_{1/2\beta}$) was calculated as $0.693/\lambda$. Mean residence time (MRT) was calculated as $AUMC/AUC_{\infty}$, where AUMC was the area under the first moment of the plasma concentration-time curve, calculated using the linear trapezoidal rule from time zero to the time of the last quantifiable plasma concentration (t_{last}) and extrapolated to infinity.

Pharmacokinetic parameters were summarized by treatment using descriptive statistics (n, arithmetic mean and standard deviation). Median and range were determined for t_{\max} .

Values of C_{\max} , AUC_{∞} , t_{first} and t_{\max} of the FBSF formulations were compared with OTFC using an ANOVA model and Tukey's multiple comparison test. Bioequivalence was tested upon 90% confidence interval (CI) for test/reference from an ANOVA of the parameters C_{\max} , AUC_{last} and AUC_{∞} . The established acceptance range for bioequivalence was 0.8–1.25. Each of the parameters was log-transformed in order to obtain a ratio of test/reference. These log-transformed values were analysed using a mixed ANOVA model with period and treatment as fixed effects and subject as random effect.

Results

Study Population

Twelve healthy subjects (nine males and three females) with a mean age of 31.6 years (range

21–44 years) and a mean bodyweight of 70.5 kg were enrolled in the study. The study population was comprised of Hispanic (42%), Caucasian (33%) and Black (25%) subjects. All 12 subjects enrolled completed the four treatments and were included in the analysis.

Pharmacokinetics

The mean plasma fentanyl concentrations over 48 hours after study dose administration are shown in figure 1. Pharmacokinetic parameters are summarized in table I. Pre-dose plasma fentanyl concentrations were measured in some subjects prior to the second, third and fourth doses of the study. These data were included in the pharmacokinetic analysis with redefinition of C_{first} as the first quantifiable plasma concentration above the pre-dose concentration.

Plasma fentanyl concentrations were observed earlier (t_{first}), and both peak concentrations (C_{\max}) and overall systemic exposure (AUC_{∞}) were higher after administration of all three of the FBSF formulations (pH 6, pH 7.25 or pH 8.5) than with OTFC (table I). The C_{\max} for the FBSF formulations exceeded that of OTFC by a range of 36–65%, and the AUC_{∞} by a range of 27–41%.

The t_{first} values for the pH 6.0 and 7.25 formulations were virtually the same (7.8 and 9 minutes, respectively); however, the pH 7.25 FBSF

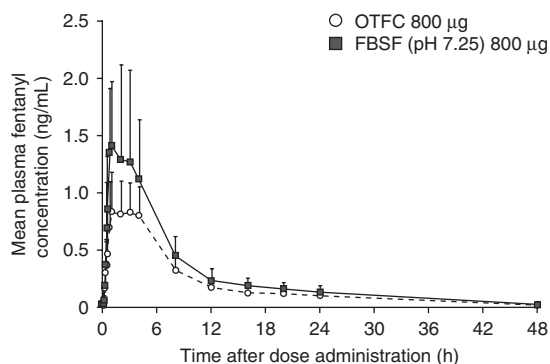


Fig. 1. A comparison of the mean (standard deviation) plasma fentanyl concentrations over 48 hours after administration of single 800 µg buccal doses of oral transmucosal fentanyl citrate (OTFC) or fentanyl buccal soluble film (FBSF) pH 7.25. Each data point reflects the mean plasma fentanyl concentrations at that particular sampling time point.

Table I. Pharmacokinetic parameters of single 800 µg doses of oral transmucosal fentanyl citrate (OTFC) and three fentanyl buccal soluble film (FBSF) formulations^a

| Parameter | OTFC 800 µg (n = 12) | pH 6 FBSF 800 µg (n = 12) | pH 7.25 FBSF 800 µg (n = 12) | pH 8.5 FBSF 800 µg (n = 12) |
|---------------------------------------|-------------------------|------------------------------|---------------------------------|--------------------------------|
| Pre-dose concentrations (ng/mL) | 0.034 ± 0.033 | 0.026 ± 0.027 | 0.037 ± 0.035 | 0.032 ± 0.030 |
| t _{first} (min) | 13.2 ± 10.8 | 7.80 ± 1.80 | 9.00 ± 4.80 | 12.0 ± 6.00 |
| C _{max} (ng/mL) ^b | 1.03 ± 0.248 | 1.4 ± 0.491 | 1.7 ± 0.754 | 1.4 ± 0.409 |
| AUC _∞ (ng • h/mL) | 10.3 ± 3.84 | 13.7 ± 4.54 | 14.5 ± 5.40 | 13.1 ± 4.77 |
| t _{max} (h) ^c | 2.0 (0.50–4.0) | 2.0 (0.75–4.0) | 1.0 (0.75–4.0) | 2.0 (0.50–4.0) |
| λ (h ⁻¹) | 0.0528 ± 0.020 | 0.0505 ± 0.0157 | 0.0502 ± 0.0109 | 0.0562 ± 0.0152 |
| t _{½β} (h) | 15.3 ± 6.85 | 15.1 ± 5.09 | 14.4 ± 2.89 | 13.3 ± 4.14 |
| MRT | 15.9 ± 6.17 | 15.7 ± 4.19 | 14.5 ± 3.23 | 14.3 ± 4.45 |

a Values are given as mean ± SD unless otherwise specified.

b Represents the mean C_{max} across all subjects' individual C_{max}, which could have occurred at any sampling time point.

c Median (range).

λ = observed terminal elimination rate constant; AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; C_{max} = maximum drug concentration in plasma; MRT = mean residence time; SD = standard deviation; t_{½β} = terminal elimination half-life; t_{first} = time to reach the first quantifiable plasma concentration above the pre-dose concentration; t_{max} = time to reach C_{max}.

formulation provided the earliest t_{max} with the highest C_{max} and AUC_∞. The mean C_{max} for pH 7.25 FBSF formulation was 65% above that of OTFC (1.7 vs 1.03 ng/mL) and the mean AUC_∞ for pH 7.25 FBSF formulation was 41% higher than that for OTFC (14.5 vs 10.3 ng • h/mL).

The differences in C_{max} were statistically significant when comparing all FBSF formulations with OTFC (p = 0.03) [table II] and for pairwise comparisons of pH 7.25 FBSF to OTFC (p < 0.05). Likewise, FBSF and OTFC were not found to be bioequivalent in terms of C_{max} (90% CI 1.38, 1.74), AUC_{last} (90% CI 1.33, 1.54) and AUC_∞ (90% CI 1.31, 1.55).

Discussion

FBSF was developed with the goal of minimizing patient participation in dosing, as well as

to produce a consistent pharmacokinetic profile. In this study, three formulations of FBSF with mucoadhesive layers buffered to different pH values were tested to select the one that provides the optimum balance between dissolution and absorption.

The three FBSF formulations produced favourable plasma fentanyl concentration-time profiles. The mean plasma fentanyl concentrations were higher with each of the three FBSF formulations than with OTFC, and the overall systemic fentanyl exposure with the FBSF formulations was also greater than with OTFC, indicating that, regardless of the pH of the mucoadhesive layer of the FBSF, the rate and extent of fentanyl absorption is greater with FBSF than with OTFC.

FBSF appeared to have the most favourable pharmacokinetics when the pH of the

Table II. ANOVA for comparing the mean differences in pharmacokinetic parameters of fentanyl buccal soluble film and oral transmucosal fentanyl citrate

| Parameter | Degrees of freedom | Sum of squares | Mean squares | F-value | p-Value |
|------------------------------|--------------------|----------------|--------------|---------|---------|
| t _{first} (min) | 3 | 0.07 | 0.02 | 1.82 | 0.16 |
| t _{max} (h) | 3 | 3.33 | 1.11 | 0.75 | 0.53 |
| C _{max} (ng/mL) | 3 | 2.54 | 0.85 | 3.26 | 0.03 |
| AUC _∞ (ng • h/mL) | 3 | 118.0 | 39.3 | 1.80 | 0.16 |

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; C_{max} = maximum drug concentration in plasma; t_{first} = time to reach the first quantifiable plasma concentration above the pre-dose concentration; t_{max} = time to reach C_{max}.

mucoadhesive layer was 7.25. This finding suggests that at pH 7.25, a balance between fentanyl dissolution and transmucosal absorption takes place, with excellent tolerability of the dose unit at the application site.^[5]

In this study, the C_{\max} , AUC_{last} and AUC_{∞} of pH 7.25 FBSF were not bioequivalent to those for OTFC, indicating that the products are not interchangeable on a per microgram dose basis.

At the time of design of the current study, the only information available on which to base the dose interval was the $t_{1/2\beta}$ reported for OTFC, which was 193–386 minutes (3.2–6.4 hours).^[4] Based on this information, a 48-hour dosing interval was selected for this study. However, the longer $t_{1/2\beta}$ of fentanyl observed in the current study (13–15 hours) was likely due to the sensitivity of the bioanalytical assay used to determine fentanyl concentrations with an LLQ of 0.0250 ng/mL (25 pg/mL). The 48-hour washout period did result in quantifiable pre-dose concentrations in subsequent dosing periods for some subjects. These data were included in the pharmacokinetic analysis with redefinition of C_{first} as the first quantifiable plasma concentration above the pre-dose concentration. Most of these pre-dose concentrations were <5% of the respective C_{\max} in the profile, and are therefore acceptable based on criteria stated in the US FDA's guidance on bioavailability/bioequivalence.^[14] Two subjects in the OTFC group had pre-dose values that were >5% of the C_{\max} value (6.8% and 6.7%). No adjustment was made for these as the conclusions were unaffected, and none of these observations compromised the study objective of selecting the most favourable formulation of FBSF.

Breakthrough pain is acute and severe, peaks in 3–5 minutes and has an average duration of 30 minutes.^[15–18] For this reason, the speed of onset and extent of analgesic effect are critical factors in the effective management of breakthrough pain. Transmucosal delivery of fentanyl provides rapid uptake of fentanyl across the mucosal membranes into the systemic circulation and can produce rapid relief of symptoms.^[19–23] Absorption of fentanyl through this route also bypasses first-pass metabolism through the

cytochrome P450 3A4 gastrointestinal and/or hepatic systems, resulting in greater bioavailability.^[24] Consistent with this, OTFC demonstrated faster relief than oral short-acting morphine in managing cancer breakthrough pain.^[25] This study supports the use of rapid delivery transmucosal technology for providing healthcare practitioners with alternatives to oral pain medications. Additional studies have been completed and/or are underway to assess the clinical effectiveness of the pH 7.25 FBSF formulation.

Conclusions

All three FBSF formulations produced greater peak plasma concentrations and overall exposure to fentanyl than OTFC in this study. In particular, the pH 7.25 FBSF formulation showed the most favourable pharmacokinetic profile of the three FBSF formulations. In comparison with OTFC, the pH 7.25 FBSF formulation produced the fastest and most efficient delivery of fentanyl and was selected for further clinical development.

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