# Stability of 10 and 50 mcg/mL Fentanyl Solutions in CADD® Reservoirs, PVC containers and Ethylene/Propylene Co-Polymer (PAB®) Bags at Refrigerated (4˚C) and Room Temperature (23˚C).

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## INTRODUCTION

Previous publications have demonstrated the stability of fentanyl solution for up to 30 days in PVC cassettes. In these studies very little degradation of fentanyl was observed.

When selecting a container for storage, water loss must be considered, since an increase in concentration has been reported to occur with PVC containers, when storage occurs over an extended period of time. Water loss can be impacted by surface area, container material and thickness, temperature and relative humidity.

Facilities without securely lockable refrigerators may store compounded narcotic infusions in a locked cabinet at room temperature, but this may enhance water loss.

Since the degree of water loss is dependent on temperature and container type AND since current regulations within Ontario require labels to identify the exact concentration, storage container type is becoming a very important determinant of product integrity and the use-before-date.

## OBJECTIVES

The objective of this study was to evaluate the stability of fentanyl concentrations of 10 mcg/mL and 50 mcg/mL in CADD reservoirs, PVC bags and PAB® bags while also evaluating water loss over a 90 day storage period at room temperature.

The concentration of fentanyl was evaluated during storage using a validated, stability indicating, liquid chromatographic method using UV detection.

### Figure 1.

Chromatogram A represents a mixture of various narcotics demonstrating the ability of the chromatographic system to separate similar compounds. Fentanyl elutes at 5 minutes and is separated from all other compounds.
Chromatogram B represents a 50 mcg/mL fentanyl solution in a PAB® bag on study day zero.
Chromatogram C represents the same 50 mcg/mL fentanyl solution in a PAB® bag following storage for 90 days at room temperature.

Note. After 90 days of storage at room temperature additional peaks are not present in the chromatogram indicating the lack of degradation of fentanyl during storage .

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The fentanyl, PAB® bags and CADD® cassettes used in this study were purchased by the Department of Pharmacy, Sunnybrook Health Sciences Centre.

### Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 28% acetonitrile and 72% 0.05 mol/L phosphoric acid which was pumped through a 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil ABZ-plus; Supelco, Toronto, Ontario) at 1.0 mL/min. The effluent was monitored at 220 nm.

### Assay Validation

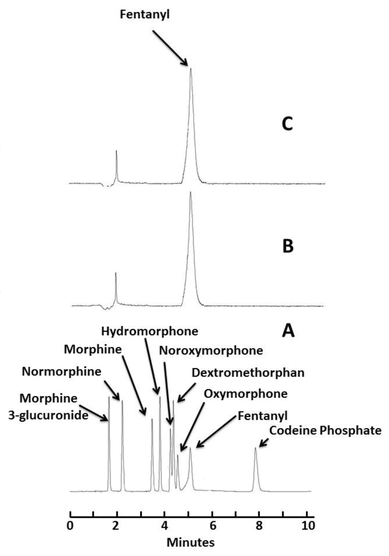
A chromatographic separation was developed and evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating fentanyl from its degradation products and other narcotics (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

### Stability Study

On study day 0, 24 x 100 mL solutions of 10 mcg/mL of fentanyl were prepared in 0.9% sodium chloride injection and 100 mL was added to each of 8 empty CADD® reservoirs, PVC bags, and PAB® bags (total of 24 containers). Four units of each container were stored at room temperature and 4 were stored at 4C. These steps were repeated with fentanyl 50 mcg/mL (undiluted drug). Concentration, physical inspection and bag weights were completed on days 0, 1, 3, 7, 14, 24, 38, 56, 76, and 90.

### Data Reduction and Statistical Analysis

Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate.




## CONCLUSIONS

Fentanyl concentrations change primarily due to water loss. Water loss was similar in both CADD® Cassettes and PVC bags, averaging 5.0 mL in 90 days at room temperature and less than 0.3 mL at 4C.

100 mL PAB® containers stored at room temperature lost less than 0.26 mL over the 90-day study period. Under refrigeration, water loss in a PAB® was negligible.

When corrected for water loss, fentanyl concentrations change by less than 1% over the 90-day study period, demonstrating the extended chemical stability of fentanyl admixtures, exceeding USP General Chapter <797> BUD limits.

When establishing a BUD in your institution, we believe that the potential for water loss should be taken into account in addition to the results of this study and the environment and procedures under which sterile compounding is completed.

## RESULTS

### Concentration Results

Concentrations on each study day are reported in Table 1 and were observed to increase by ~6% in PVC Cassettes and PVC bags and by ~1% in PAB® containers at the end of study period (90 days) when stored at room temperature.

Nonetheless, the calculated use-before-date, with 95% confidence, averaged 553 days, exceeding the 90 study period for all containers, concentrations and temperatures.

When corrected for water loss, fentanyl concentrations change by less than 1% over the 90-day study period.

### Assay Validation

Assay validation demonstrated that numerous other narcotics are separated from fentanyl (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.46% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.93% within a day and 2.48% between days.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$), container ($p < 0.001$), and temperature ($p<0.001$) but cot concentration ( $p = 0.9877$). The study was capable of detecting a 0.81% difference in concentration due to study day, temperature, concentration or container. The difference due to container or temperature is about 1%.

### Table 1. Percent Remaining of the Initial Fentanyl Concentration.

| Study Day | CADD Cassette 4C 10 mcg/mL | CADD Cassette RT 10 mcg/mL | PVC Bag 4C 10 mcg/mL | PVC Bag RT 10 mcg/mL | PAB Bag 4C 10 mcg/mL | PAB Bag RT 10 mcg/mL | CADD Cassette 4C 50 mcg/mL | CADD Cassette RT 50 mcg/mL | PVC Bag 4C 50 mcg/mL | PVC Bag RT 50 mcg/mL | PAB Bag 4C 50 mcg/mL | PAB Bag RT 50 mcg/mL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| 1 | 100.31 | 100.17 | 99.99 | 100.08 | 100.08 | 100.49 | 100.11 | 99.33 | 100.30 | 100.73 | 99.78 | 99.94 |
| 3 | 100.02 | 100.15 | 100.04 | 100.23 | 100.17 | 99.90 | 100.06 | 99.74 | 100.40 | 100.44 | 100.17 | 100.18 |
| 7 | 99.94 | 100.47 | 99.98 | 100.74 | 99.92 | 100.12 | 99.99 | 100.22 | 100.02 | 100.45 | 99.34 | 99.90 |
| 14 | 100.37 | 100.88 | 100.01 | 101.13 | 99.95 | 99.94 | 100.11 | 101.43 | 100.08 | 101.11 | 99.92 | 100.11 |
| 24 | 98.66 | 101.17 | 99.87 | 101.41 | 98.27 | 100.61 | 98.36 | 99.65 | 101.20 | 100.41 | 99.99 | 99.89 |
| 38 | 100.08 | 102.00 | 100.52 | 102.77 | 100.81 | 100.79 | 100.08 | 102.40 | 100.48 | 102.55 | 99.96 | 100.69 |
| 56 | 100.13 | 103.81 | 99.90 | 103.61 | 99.93 | 100.01 | 100.48 | 103.29 | 100.57 | 103.70 | 100.30 | 100.28 |
| 76 | 99.83 | 103.95 | 100.58 | 104.13 | 100.49 | 100.45 | 100.25 | 105.69 | 100.24 | 105.28 | 100.02 | 100.58 |
| 90 | 100.79 | 105.81 | 100.32 | 106.10 | 100.25 | 101.54 | 100.40 | 105.89 | 100.29 | 106.26 | 100.02 | 100.48 |
| Change in Concentration (%/Day) | 0.004 | 0.060 | 0.005 | 0.062 | 0.005 | 0.010 | 0.005 | 0.072 | 0.002 | 0.067 | 0.003 | 0.007 |
| Std Dev of Regression (Sy.x) | 0.567 | 0.336 | 0.213 | 0.329 | 0.684 | 0.412 | 0.601 | 0.732 | 0.370 | 0.507 | 0.251 | 0.207 |
| T-90 - Days) | 2587.3 | 165.5 | 2096.9 | 161.9 | 2035.8 | 1000.4 | 1872.95 | 138.3 | 6437.6 | 149.1 | 3445.3 | 1502.0 |
| Shortest T-90 (95% CI) - Days | 584.6 | 146.5 | 1026.2 | 143.9 | 478.5 | 509.6 | 515.9 | 181.8 | 980.3 | 126.8 | 1141.7 | 869.4 |
| Weight Loss over 90 days (gm ≈ mL) | 0.15 | 5.00 | 0.31 | 4.75 | 0.00 | 0.26 | 0.28 | 5.36 | 0.32 | 5.07 | 0.04 | 0.18 |
| Change in Concentration (%/Day) AFTER Correction for Weight Loss | 0.002 | 0.002 | 0.001 | 0.006 | 0.005 | 0.007 | 0.002 | 0.008 | -0.002 | 0.007 | 0.002 | 0.005 |
| Shortest T-90 AFTER Correction for Water Loss [95% CI] - Days | 649.9 | 1014.5 | 1598.4 | 706.0 | 478.5 | 601.0 | 615.8 | 398.8 | 1508.4 | 519.4 | 1201.8 | 1062.9 |