Stability of 0.05 mg/mL Sufentanil Solutions In CADD® Reservoirs, PVC containers, Ethylene/Propylene Co-Polymer (PAB®) Bags and Syringes at Room Temperature (23˚C).

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INTRODUCTION

Previous publications have demonstrated the stability of sufentanil solution in polypropylene syringes for 30 days <Jappinen et al. Eur J Pharm Sci 2003.> and for up to 70 days at 4C in PVC containers <Boitquin et al. Ann Pharmacother 2004> when mixed with levobupivacaine in saline at 1 mcg/mL.

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 determinate of product integrity and the use-before-date.

OBJECTIVES

The objective of this study was to evaluate the stability of sufentanil concentrations of 50 mcg/mL in CADD reservoirs, PVC bags, PAB® bags and Polypropylene Syringes while also evaluating water loss over a 90 day storage period at room temperature and 4C.

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

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Sufentanil, PAB® bags, PVC Bags, CADD® reservoirs and all supplies used in this study were purchased and funded by the Department of Pharmacy, Sunnybrook Health Sciences Centre.

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 30% acetonitrile and 70% 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 288 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.

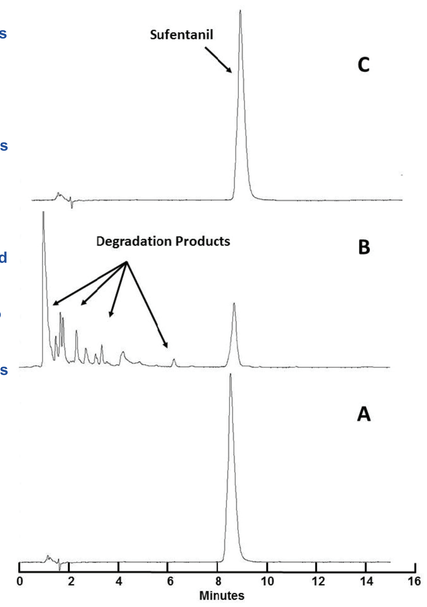
Stability Study

On study day 0, 50 mL solutions of 50 mcg/mL of sufentanil were prepared without dilution and added directly to empty PVC bags, CADD cassettes, PAB® bags and Polypropylene Syringes. 4 units of each container combination were prepared and stored at room temperature (23C). An additional 4 CADD Cassettes were stored at 4C. Concentration, physical inspection and container weights were completed on days 0, 1, 4, 7, 14, 21, 35, 56, 70, 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.

Figure 1.
Chromatogram A represents a solution of 25 mcg/mL sufentanil in water prior to the addition of sodium hypochlorite at room temperature (23C). Chromatogram B represents the same sample immediately after the addition of 4% sodium hypochlorite. 28.9% of the initial sufentanil concentration was observed to remain. Several degradation products appear and all elute prior to the sufentanil peak, which elutes at 8.9 minutes. Chromatogram C represents the a 50 mcg/mL sufentanil solution in a PAB® bag on study day 90. Note that none of the degradation products observed in the accelerated study (eluting prior to 6 minutes) were observed after 90 days storage at room temperature.



CONCLUSIONS

Sufentanil concentrations in CADD Cassettes and PVC bags change primarily due to water loss. Water loss was similar in both CADD® Cassettes (5.7 mL in a 50 mL cassette) and 6.8 mL from a 50 mL PVC bags. Loss in the CADD Cassette was reduced to 0.4 mL from a 50 mL Cassette during storage at 4C.

50 mL PAB® containers stored at room temperature lost less than 0.4 mL over the 90-day study period. Under refrigeration, water loss in a PAB® was negligible.

When corrected for water loss, sufentanil concentrations change by less than 4% over the study period and the use-before-date, with 95% confidence, was greater than 139 days, 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 more than 15% in CADD PVC Cassettes and PVC bags stored at room temperature. Storage in PAB bags and syringes at 23C or CADD Cassettes stored at 4C was similar.

The calculated use-before-date, with 95% confidence, was 52-60 days for CADD Cassettes and PVC bags. However, when corrected for water loss, the concentration changed by less than 4% over the 90-day study period.

Assay Validation

Assay validation demonstrated that degradation products are separated from sufentanil (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.44% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 1.06% within a day and 2.14% between days.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$), container ($p < 0.001$), and temperature ($p<0.001$). The study was capable of detecting a 1.9% difference in concentration.

Table 1. Percent Remaining of the Initial Sufentanil Concentration.

Study Days	CADD Cassette RT 50ug/mL	CADD Cassette 4C 50ug/mL	PVC Bag RT 50ug/mL	PAB Bag RT 50ug/mL	Syringe RT 50ug/mL
0	100.00	100.00	100.00	100.00	100.00
1	101.99	100.72	102.19	100.16	100.95
4	102.11	99.84	102.51	100.14	101.02
7	102.47	99.83	102.66	100.38	101.60
14	103.14	98.70	103.68	97.24	97.32
21	103.83	101.70	106.18	101.98	99.38
35	106.66	103.04	107.81	102.77	101.79
56	109.35	101.86	110.37	101.94	101.64
70	113.76	103.21	114.99	103.23	102.69
90	115.38	102.80	118.84	103.40	103.76
Change in Concentration (%/Day)	**0.164**	**0.039**	**0.190**	**0.045**	**0.037**
Std Dev of Regression (Sy.x)	0.782	1.043	0.872	1.339	1.419
T-90 (Days)	60.9	259.1	52.5	224.6	266.8
Shortest T-90 (95% CI)	**54.7**	**157.0**	**47.3**	**130.3**	**139.6**
Weight Loss (gm over 90 days ~ mL)	**5.70**	**0.39**	**6.84**	**0.37**	**0.00**
Change in Concentration AFTER Correction for Weight Loss (%/Day)	**0.017**	**0.030**	**0.004**	**0.036**	**0.037**
Shortest T-90 AFTER Correction for Weight Loss [95% CI] (%/Day)	**276.4**	**182.6**	**392.6**	**147.3**	**139.6**