Stability of 0.2 and 10 mg/mL Hydromorphone Solutions In CADD® reservoirs, PVC and Ethylene/Propylene Co-Polymer (PAB®) Bags at Room Temperature (23˚C).

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INTRODUCTION

Numerous studies report the stability of hydromorphone, although most report the stability of hydromorphone in combination with other medications.

Four studies report the stability of hydromorphone alone. These studies demonstrate stability after 4 months storage at 37C in an implantable infusion system <Hildebrand et al. J Pain Sympt Management; 2001>, after 30 days storage at 30C in syringes <Stiles AJHP 1996>, after 72 hours at 24C in PVC bags <Christen AJHP 1996> and after 42 days storage at either 4C or 23C in PVC bags<Walker CJHP 1988>. When considering PVC storage containers only, stability is reported for concentration of 0.02 and 0.1 mg/mL for only 72 hours and stability of concentrations between 1 and 5 mg/mL has been reported for 42 days.

In these studies very little degradation was observed, although an increase in concentration of between 3-5%, likely due to water loss, was reported over the 42-day study period when PVC bags are stored at room temperature (Walker CJHP 1988).

Furthermore, facilities without securely lockable refrigerators may store compounded narcotic infusions in a locked cabinet at room temperature which 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 hydromorphone concentrations at lower (0.2 mg/mL) and higher (10 mg/mL) than previously reported in CADD reservoirs, PVC bags and PAB® bags while also evaluating water loss over a 90 day storage period at room temperature and 4°C.

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

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The hydromorphone, PVC bags, PAB® bags and CADD® cassettes used in this study were purchased by the Department of Pharmacy, Sunnybrook Health Sciences Centre.

METHODS

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; 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 hydromorphone from its degradation products (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.

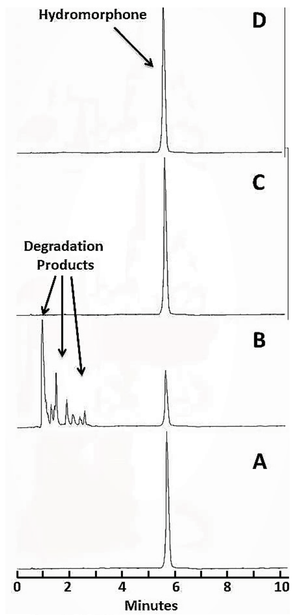
Stability Study

On study day 0, 100 mL solutions of 0.2 mg/mL and 10mg/mL concentrations of hydromorphone were prepared in saline. Four units of each solution were stored at room temperature. Concentration, physical inspection and bag weights were completed on study 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.

Figure 1.
Chromatogram A represents a solution of 1.0 mg/mL hydromorphone in water at pH 8.3 prior to incubation at 91 C. Chromatogram B represents the same sample after 215 hours incubation at 91C. 39% of the initial hydromorphone concentration was observed to remain. Several degradation products appear and all elute prior to the hydromorphone peak, which elutes at 5.6 minutes. Chromatogram C represents a 10 mg/mL hydromorphone solution in a PAB® bag on study day 0. Chromatogram D represents the same 10 mg/mL hydromorphone solution in a PAB® bag on study day 90. Note that none of the degradation products observed in the accelerated study (eluting prior to 3 minutes) were observed after 90 days storage at room temperature.



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CONCLUSIONS

Hydromorphone concentrations change primarily due to water loss. Water loss averages ~5.8 mL over 90 days from 100 mL PVC containers within CADD® PVC reservoirs and 7.9 mL from PVC 100 mL minibags.

100 mL PAB® containers lost less than 0.4 mL over the 90-day study period when stored at room temperature.

When corrected for water loss, hydromorphone concentrations change by less than 0.5% over the 90-day study period.

The results of this study demonstrate extended chemical stability of hydromorphone 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, CADD (PVC) reservoirs, ~8% in PVC bags and by ~1% in PAB® containers. Even so, the calculated use-before-date, with 95% confidence, averaged 404 days, exceeding the 90 study period for all containers.

Assay Validation

Assay validation demonstrated that degradation products are separated from hydromorphone) (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.52% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 1.04% within a day and 1.31% between days.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$) and container ($p < 0.001$) but not concentration ($p = 0.4478$). The study was capable of detecting a 0.92% difference in concentration due to study day, concentration or container. The average difference due to concentration is 0.24%.

Table 1. Percent Remaining of the Initial Hydromorphone Concentration.

Study Day	100 mL PVC Cassette 0.2 mg/mL	100 mL PVC Cassette 10 mg/mL	100 mL PVC Bag 0.2 mg/mL	100 mL PVC Bag 10 mg/mL	100 mL PAB Bag 0.2 mg/mL	100 mL PAB Bag 10 mg/mL
0	100.00	100.00	100.00	100.00	100.00	100.00
1	99.82	100.06	99.76	100.11	100.26	100.02
3	99.56	100.16	100.10	100.20	99.31	99.98
7	99.66	100.43	100.24	100.54	99.48	100.06
14	100.07	100.87	100.93	101.01	99.32	100.10
24	101.27	101.27	100.89	101.83	99.87	100.14
38	101.57	102.33	102.93	102.99	99.90	100.14
56	103.65	103.61	104.24	104.51	99.76	100.27
76	104.65	105.07	106.34	106.22	100.47	100.35
90	105.62	105.50	108.82	107.72	101.01	100.60
Change in concentration (%/Day)	0.0678	0.0637	0.0936	0.0841	0.0113	0.0056
Std Dev of Regression (Sy.x)	0.350	0.148	0.534	0.128	0.404	0.055
T-90 (Days)	147.5	156.9	106.9	118.8	881.9	1787.1
Shortest T-90 [95% CI]- (Days)	131.6	148.8	94.3	114.8	481.5	1453.8
Weight loss (mL - %)/day	0.0636	0.0645	0.0757	0.0778	0.0040	0.0042
Change in Concentration AFTER Correction for Wt Loss (%/Day)	0.0042	-0.0008	0.0178	0.0063	0.0074	0.0014
Shortest T-90 [95% CI] (Days)	807.0	2371.3	329.8	1071.3	595.6	3741.1