Stability and Compatibility of Bupivacaine and Hydromorphone in PVC and non-DEHP bags for 30 days at 4°C and 25°C

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INTRODUCTION

While there have been previous studies that demonstrated stability and compatibility of hydromorphone and bupivacaine, none have evaluated the stability and compatibility at low hydromorphone concentrations when stored in PVC or non-DEHP bags.

OBJECTIVES

The objective of the study was to evaluate the stability and compatibility of four concentration combinations of bupivacaine and hydromorphone diluted in 0.9% sodium chloride and stored in PVC bags and non-DEHP bags for 30 days at 4°C and 25°C.

The concentrations of bupivacaine and hydromorphone were evaluated during storage at each temperature and container using a validated, stability indicating, liquid chromatographic method using UV detection.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 20% acetonitrile and 80% 0.05M phosphoric acid which was pumped through 150mm x 4.6mm reverse-phase C18, 5µm column (Supelcosil ABZ+; Supelco, Toronto, ON) at 1.0 mL/min and held at a temperature of 35°C. The effluent was monitored with UV detection at 210nm.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating hydromorphone and bupivacaine from each other and their respective 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 (CV) and the standard deviation of regression.

Stability Study

On study day 0, eight Baxter PVC bags and eight Fresenius Kabi non-DEHP bags were prepared using bupivacaine (SteriMax; lot B5E0008A; expiry Dec-2023) and hydromorphone (Sandoz; lot 6024334; expiry: Jun-2023) diluted in 0.9% sodium chloride according to the following concentration combinations bupivacaine 0.5mg/mL and hydromorphone 1.5mcg/mL; bupivacaine 0.5mg/mL and hydromorphone 30mcg/mL; bupivacaine 2.5mg/mL and hydromorphone 1.5mcg/mL; bupivacaine 2.5mg and hydromorphone 30mcg/mL. Four bags of each were stored at 4°C (refrigerator) and 25°C (room temperature). Concentration and physical inspection were completed on days 0, 2, 7, 9, 14, 21, and 30.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration.

Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the *a priori* cut-off for significance.

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RESULTS

Table 1. Concentrations[1] of Bupivacaine and Hydromorphone in Baxter PVC bags stored at 4°C

	Combination 1		Combination 2		Combination 3		Combination 4	
Drug	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)
Nominal Initial Concentration	0.5	1.5	0.5	30	2.5	1.5	2.5	30
Actual Initial Concentration	0.52 ± 0.01	1.59 ± 0.04	0.52 ± 0.01	30.69 ± 0.10	2.58 ± 0.01	1.58 ± 0.03	2.55 ± 0.02	30.87 ± 0.20
Study Day 2	100.61 ± 0.19	98.28 ± 2.84	100.58 ± 0.50	99.09 ± 0.85	100.59 ± 0.10	101.37 ± 1.82	100.60 ± 0.54	100.17 ± 0.83
Study Day 7	98.53 ± 0.20	100.56 ± 3.10	98.55 ± 0.53	99.30 ± 1.16	98.59 ± 0.27	101.57 ± 1.11	98.49 ± 0.06	98.83 ± 0.47
Study Day 9	100.25 ± 0.61	101.50 ± 2.71	100.05 ± 0.42	100.74 ± 1.35	100.03 ± 0.58	102.44 ± 1.34	100.47 ± 0.67	101.66 ± 0.89
Study Day 14	101.29 ± 0.35	98.74 ± 5.21	100.71 ± 0.80	100.02 ± 1.30	101.28 ± 0.34	101.19 ± 2.25	103.01 ± 0.65	100.26 ± 1.13
Study Day 21	99.77 ± 0.34	96.89 ± 2.08	99.33 ± 0.48	100.27 ± 0.46	99.73 ± 0.23	100.09 ± 1.86	101.68 ± 0.79	99.87 ± 0.90
Study Day 30	98.78 ± 1.07	97.87 ± 2.64	98.42 ± 0.49	100.41 ± 0.48	98.63 ± 0.11	99.14 ± 3.10	100.05 ± 0.86	99.99 ± 0.66
Degradation Rate (%/day)	-0.031	-0.087	-0.047	0.029	-0.034	-0.059	0.033	-0.002
Sy.x	1.006	1.461	0.847	0.550	0.995	1.028	1.505	0.910
Std Error in Slope	0.038380	0.055732	0.032324	0.020979	0.037951	0.039220	0.057420	0.034708
Confidence interval for slope	0.09866	0.14326	0.08309	0.05393	0.09756	0.10082	0.14760	0.08922
Fastest Slope 95% Confidence	-0.1293060	-0.2305269	-0.1296335	-0.024483	-0.1320115	-0.159644	-0.1143809	-0.091530
Shortest T-90 (95% CI) in days	**77.34**	**43.38**	**77.14**	**408.45**	**75.75**	**62.64**	**87.43**	**109.25**

[1]: Concentrations expressed as percent remaining ± coefficient of variation.

Table 2: Concentrations[1] of Bupivacaine and Hydromorphone in Fresenius Kabi non-DEHP bags stored at 4°C

	Combination 1		Combination 2		Combination 3		Combination 4	
Drug	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)
Nominal Initial Concentration	0.5	1.5	0.5	30	2.5	1.5	2.5	30
Actual Initial Concentration	0.52 ± 0.01	1.62 ± 0.02	0.52 ± 0.01	30.72 ± 0.10	2.57 ± 0.03	1.61 ± 0.01	2.56 ± 0.01	31.01 ± 0.16
Study Day 2	100.71 ± 0.14	97.07 ± 0.59	100.72 ± 0.45	98.72 ± 0.75	100.73 ± 1.10	99.29 ± 0.60	100.91 ± 0.49	99.70 ± 0.74
Study Day 7	98.43 ± 0.12	98.12 ± 2.25	98.56 ± 0.40	98.91 ± 0.69	98.75 ± 0.44	100.27 ± 0.78	98.44 ± 0.12	100.01 ± 0.27
Study Day 9	100.31 ± 0.18	99.55 ± 1.16	100.46 ± 0.38	100.64 ± 0.53	100.39 ± 0.59	101.35 ± 0.05	100.62 ± 0.68	101.54 ± 0.46
Study Day 14	101.56 ± 0.28	99.00 ± 1.33	101.20 ± 0.58	99.95 ± 0.43	102.12 ± 0.60	100.34 ± 0.46	102.36 ± 0.61	99.47 ± 1.06
Study Day 21	99.77 ± 0.04	97.09 ± 2.41	99.74 ± 0.64	99.79 ± 0.22	100.81 ± 0.47	99.23 ± 2.12	101.16 ± 0.55	98.86 ± 0.57
Study Day 30	97.98 ± 0.39	97.00 ± 1.11	99.01 ± 0.70	99.93 ± 0.13	99.16 ± 0.83	96.92 ± 1.76	99.70 ± 0.44	99.49 ± 0.56
Degradation Rate (%/day)	-0.052	-0.064	-0.028	0.019	-0.008	-0.088	0.010	-0.032
Sy.x	1.229	1.166	0.975	0.700	1.227	1.126	1.353	0.831
Std Error in Slope	0.046896	0.044503	0.037187	0.026712	0.046808	0.042955	0.051616	0.031707
Confidence interval for slope	0.12055	0.11440	0.09559	0.06866	0.12032	0.11042	0.13268	0.08150
Fastest Slope 95% Confidence	-0.1724072	-0.178270	-0.1235693	-0.049887	-0.1284462	-0.198240	-0.1223018	-0.113841
Shortest T-90 (95% CI) in days	**58.00**	**56.09**	**80.93**	**200.45**	**77.85**	**50.44**	**81.76**	**87.84**

[1]: Concentrations expressed as percent remaining ± coefficient of variation.

Figure 1. Representative Chromatograms

Chromatogram A represents a solution of hydromorphone on day 0 and Chromatogram B represents a sample after degradation with sodium hydroxide (pH 8.4) and heat (90°C) for 280 hours with 24.6% remaining. Hydromorphone eluted at 2 minutes and degradation products eluted at 1-1.8min, 2.3, 2.4 and 2.8min.

Chromatogram C represents a solution of bupivacaine on day 0 and Chromatogram D represents a sample after degradation with 0.5% sodium hypochlorite with 33.41% remaining. Bupivacaine eluted at 4 min and the degradation product eluted at 6.2 min.

Chromatograms E and F represent samples taken from the Baxter PVC bag containing bupivacaine 2.5 mg/mL and hydromorphone 30 mcg/mL at 25°C on day 30. A 100 µL sample for injected to measure hydromorphone (E) and a 10 µL sample was injected to measure bupivacaine (F). No degradation products were noted. The two chromatograms were cropped and recombined at the 3 min mark for brevity.

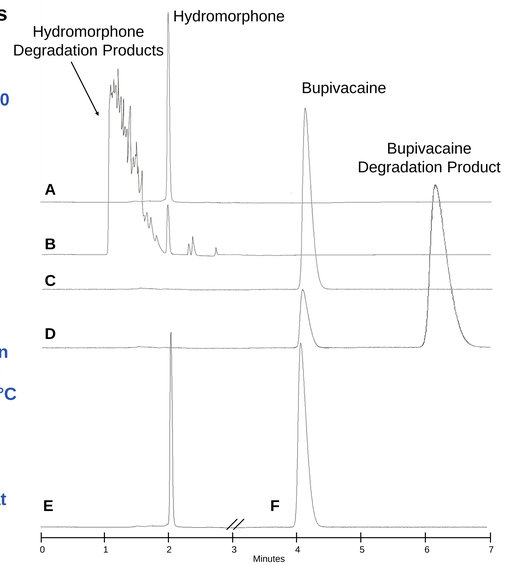

Table 3: Concentrations[1] of Bupivacaine and Hydromorphone in Baxter PVC bags stored at 25°C

	Combination 1		Combination 2		Combination 3		Combination 4	
Drug	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)
Nominal Initial Concentration	0.5	1.5	0.5	30	2.5	1.5	2.5	30
Actual Initial Concentration	0.52 ± 0.01	1.60 ± 0.01	0.52 ± 0.01	30.37 ± 0.50	2.58 ± 0.01	1.60 ± 0.01	2.58 ± 0.01	30.63 ± 0.05
Study Day 2	100.38 ± 0.78	97.63 ± 0.52	100.75 ± 0.13	100.25 ± 2.05	100.99 ± 0.20	97.33 ± 0.59	101.36 ± 0.34	100.79 ± 0.38
Study Day 7	98.45 ± 0.18	97.85 ± 1.81	98.76 ± 0.48	100.00 ± 2.28	98.45 ± 0.08	97.75 ± 2.74	99.25 ± 0.79	100.70 ± 0.87
Study Day 9	99.63 ± 1.00	100.91 ± 0.25	99.98 ± 0.96	101.70 ± 2.78	100.52 ± 0.78	99.04 ± 1.21	100.46 ± 0.19	102.02 ± 0.36
Study Day 14	100.68 ± 0.35	100.56 ± 1.25	101.30 ± 0.81	100.55 ± 2.98	102.38 ± 1.59	98.58 ± 1.50	101.97 ± 0.13	101.82 ± 0.76
Study Day 21	99.40 ± 0.30	100.64 ± 0.39	99.78 ± 0.50	100.53 ± 3.26	99.64 ± 0.38	98.74 ± 0.17	100.39 ± 0.12	101.37 ± 0.78
Study Day 30	97.87 ± 0.25	100.61 ± 0.16	98.51 ± 0.50	97.69 ± 1.83	98.39 ± 0.78	99.20 ± 0.11	98.85 ± 0.32	101.31 ± 0.97
Degradation Rate (%/day)	-0.055	0.072	-0.040	-0.063	-0.045	0.016	-0.035	0.034
Sy.x	0.906	1.277	0.984	1.101	1.457	0.965	1.130	0.656
Std Error in Slope	0.034588	0.048714	0.037551	0.042022	0.055597	0.036831	0.043124	0.025035
Confidence interval for slope	0.08891	0.12522	0.09653	0.10802	0.14292	0.09468	0.11085	0.06435
Fastest Slope 95% Confidence	-0.1439153	-0.053441	-0.1365727	-0.170797	-0.1881596	-0.078827	-0.1458450	-0.030562
Shortest T-90 (95% CI) in days	**69.49**	**187.12**	**73.22**	**58.55**	**53.15**	**126.86**	**68.57**	**327.21**

[1]: Concentrations expressed as percent remaining ± coefficient of variation.

Table 4: Concentrations[1] of Bupivacaine and Hydromorphone in Fresenius Kabi non-DEHP bags stored at 25°C

	Combination 1		Combination 2		Combination 3		Combination 4	
Drug	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)	Bupivacaine (mg/mL)	Hydromorphone (µg/mL)
Nominal Initial Concentration	0.5	1.5	0.5	30	2.5	1.5	2.5	30
Actual Initial Concentration	0.52 ± 0.01	1.60 ± 0.01	0.52 ± 0.01	30.57 ± 0.35	2.58 ± 0.01	1.59 ± 0.01	2.58 ± 0.01	30.73 ± 0.15
Study Day 2	100.89 ± 0.17	98.37 ± 0.82	100.82 ± 0.04	100.16 ± 0.92	100.80 ± 0.18	98.62 ± 1.90	101.24 ± 0.38	100.57 ± 0.74
Study Day 7	98.27 ± 0.30	98.60 ± 1.21	98.16 ± 0.15	99.61 ± 0.12	98.55 ± 0.16	98.60 ± 1.63	99.31 ± 0.68	100.30 ± 0.83
Study Day 9	99.41 ± 0.44	101.08 ± 1.07	100.16 ± 0.26	102.06 ± 1.04	100.40 ± 0.34	98.34 ± 3.28	100.64 ± 1.59	101.66 ± 0.86
Study Day 14	100.47 ± 0.37	98.95 ± 0.95	101.28 ± 0.05	100.41 ± 0.89	101.51 ± 0.10	100.30 ± 0.21	101.82 ± 1.49	101.06 ± 1.18
Study Day 21	99.28 ± 0.80	98.87 ± 0.79	99.02 ± 1.18	100.58 ± 1.11	100.17 ± 0.30	99.47 ± 0.70	100.47 ± 1.78	101.25 ± 1.15
Study Day 30	97.48 ± 0.50	99.11 ± 0.85	97.99 ± 0.18	99.77 ± 0.90	98.50 ± 0.06	99.92 ± 0.72	98.43 ± 0.92	101.26 ± 0.36
Degradation Rate (%/day)	-0.073	-0.013	-0.062	-0.005	-0.036	0.028	-0.045	0.036
Sy.x	1.007	1.022	1.199	0.893	1.146	0.801	1.140	0.497
Std Error in Slope	0.038427	0.039003	0.045742	0.034083	0.043726	0.030562	0.043510	0.018958
Confidence interval for slope	0.09878	0.10026	0.11758	0.08761	0.11240	0.07856	0.11185	0.04873
Fastest Slope 95% Confidence	-0.1715257	-0.113228	-0.1790904	-0.092978	-0.1479573	-0.050371	-0.1568950	-0.012756
Shortest T-90 (95% CI) in days	**58.30**	**88.32**	**55.84**	**107.55**	**67.59**	**198.53**	**63.74**	**783.92**

[1]: Concentrations expressed as percent remaining ± coefficient of variation.

Assay Validation

Assay validation demonstrated that degradation products are separated from bupivacaine and hydromorphone (Figure 1). Both bupivacaine and hydromorphone were measured specifically, accurately (deviations from known averaged 1.03% and 2.72%), and reproducibly (within day replicate error averaged 0.21% and 0.28%; between day replicate error averaged 0.67% and 1.22%). The standard deviation of regression averaged 1.13% for bupivacaine and 0.94% for hydromorphone.

Concentration Results

Concentrations on each study day are reported in Tables 1, 2, 3 and 4. All solutions stored at room temperature (25°C), in the refrigerator (4°C), retained more than 95% of the initial concentration for the entire study duration for all concentration combinations and container. The calculated expiry date exceeded the 30 day study period with 95% confidence for all storage conditions. Analysis of variance revealed significant differences in percent remaining due to study day ($p<0.01$), temperature ($p=0.02$) and initial bupivacaine concentration ($p<0.01$) affected percent remaining but bag material did not ($p=0.91$). For hydromorphone, study day ($p<0.01$) and initial hydromorphone concentration ($p<0.01$) affected percent remaining while temperature ($p=0.19$)and bag material did not ($p=0.12$). The study was capable of detecting a 1.05% difference in concentration due to study day, temperature, concentration or bag material.

CONCLUSIONS

Bupivacaine and Hydromorphone are stable and compatible for at least 30 days when stored at 4°C or 25°C in Baxter PVC or Fresenius Kabi non-DEHP bags.