Stability of Celestone® Soluspan® stored in Polypropylene Syringes for 210 Days at Room Temperature with Protection from Light

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INTRODUCTION

Antenatal corticosteroids are given to preterm infants to decrease infant mortality and morbidity. However, the neonatal benefits decrease with increasing gestational age and antenatal corticosteroid use may be risks for long term neurodevelopmental harm.

There is still equipoise on the optimal antenatal corticosteroid dose. The Single Dose of Antenatal Corticosteroids (SNACS) Study is seeking to evaluate if outcomes for neonates who receive 1 dose are non-inferior to those who receive 2 doses of Celestone® Soluspan®, an injectable suspension containing 3 mg/mL betamethasone acetate and 3 mg/mL betamethasone sodium phosphate. Having the Celestone® Soluspan® in prepackaged, ready-to-administer syringes on the unit is important for the timely administration of the medication.

Currently, there is no stability data available for Celestone® Soluspan® when repackaged into a polypropylene syringe and stored at room temperature.

OBJECTIVES

The objective of the study was to evaluate the physical and chemical stability of Celestone® Soluspan® repackaged in polypropylene syringes and stored at room temperature with protection from light over 210 days.

METHODS

Liquid Chromatographic Method

The liquid chromatographic (LC) methods were adapted and revalidated using a previously published protocol. The LC system was composed of a solvent delivery pump and autoinjector system (Waters Alliance 2695 Separations Module, Waters Scientific, Toronto ON) which pumped the mobile phase gradient through a 150mm x 4.6mm reverse-phase C18, 3µm column (Avantor ACE3, VWR, Mississauga, ON). The effluent was monitored with UV detection (Waters 998 photodiode array detector, Waters Scientific, Toronto ON) at 254 nm.

Mobile Phase A consisted of 1,4-dioxane:tetrahydrofuran:aqueous solution at 4:4:92 (v/v/v) and Mobile Phase B consisted of 1,4-dioxane:tetrahydrofuran:aqueous solution at 14:28:58 (v/v/v). The mobile phases were pumped in a linear gradient from 0% to 100% Mobile Phase B over 60 minutes at a flow rate of 1.0 mL/min and the column temperature held at 40°C.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating betamethasone acetate and betamethasone sodium phosphate 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, 50x 3 mL polypropylene syringes were each filled with 2 mL of Celestone® Soluspan® (lot: W007348, expiry: 2023-Jn-06) then stored at room temperature (15-30°C) with protection from light over 210 days. Physical inspection and concentration analysis were completed on study days 0, 15, 30, 60, 90, 120, 150, 180, and 210. The pH was measured on study days 0, 60, 150, and 210. On each study day, standard curves were prepared with betamethasone sodium phosphate USP reference standard (lot: R10160) and betamethasone acetate USP reference standard (lot: R11420).

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.

RESULTS

Table 1. Percent Remaining of Initial Betamethasone Acetate and Betamethasone Sodium Phosphate Concentrations[1]

		Betamethasone Acetate	Betamethasone Sodium Phosphate	Measured pH
Nominal concentration (mg/mL)		3.00	3.00	
Initial concentration (mg/mL)		2.97	3.13	
Study Day	0	100.000	100.00	7.365
	15	97.52 ± 0.68	97.58 ± 0.35	
	30	99.02 ± 1.05	98.99 ± 0.67	
	60	97.80 ± 0.73	102.27 ± 0.71	7.370
	90	100.80 ± 1.01	101.72 ± 0.65	
	120	97.80 ± 0.72	97.44 ± 0.59	
	150	97.00 ± 0.15	96.76 ± 0.57	7.391
	180	96.17 ± 0.26	99.14 ± 0.51	
	210	98.17 ± 0.57	97.16 ± 1.01	7.616
Rate of Change of Concentration (%/day)		-0.009	-0.010	
Intercept		99.141	100.002	
Standard Deviation of Regression (Sy.x)		1.365	1.964	
Std Error in Slope		0.006433	0.009259	
Confidence Interval for slope		0.01521	0.02189	
Fastest Slope 95% Confidence		-0.0246	-0.0324	
Time to achieve 90% of Initial Concentration with 95% Confidence		407.06	309.07	

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

Assay Validation

Assay validation demonstrated that betamethasone acetate and betamethasone sodium phosphate were separated from each other as well as their respective degradation products (Figure 1).

Betamethasone acetate and betamethasone sodium phosphate were measured specifically, accurately (deviations from known averaged 1.11% and 1.37%, respectively), and reproducibly (within day variation averaged 0.31% and 0.28%; between day variation averaged 1.07% and 1.05%). The standard deviation of the study samples, a second estimate of between day reproducibility, averaged 1.36% for betamethasone acetate and 1.96% for betamethasone sodium phosphate. Therefore, the assay was determined to be stability indicating.

Concentration Results

Concentrations on each study day are reported in Table 1. Both betamethasone acetate and betamethasone sodium phosphate retained at least 96% of their initial concentration for the 210 day study duration. Inspection of the chromatograms did not identify any degradation products on any of the study days. There was no precipitation, evolution of gas, or changes in colour noted. The calculated time to achieve 90% of the initial concentration with 95% confidence exceeded the 210 study day duration for betamethasone acetate and betamethasone sodium phosphate.

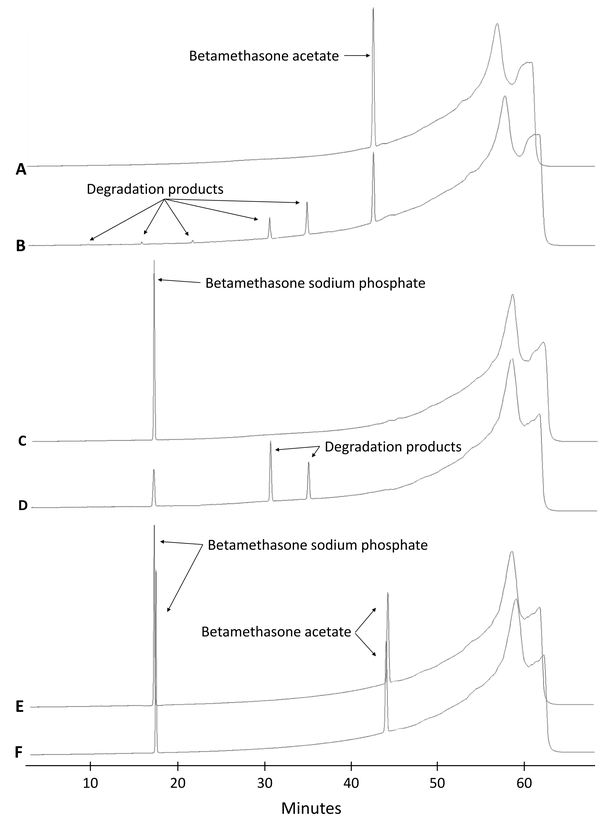

Figure 1: Representative chromatograms.

Chromatogram A shows Betamethasone acetate USP standard 0.15 mg/mL solution at time 0 and Chromatogram B shows the same sample after degradation with heat (90°C) for 24 hours with 59.8% of the initial concentration remaining. Degradation products eluted at 9.5, 15.5, 21.5, 30.5, and 35 minutes. Chromatogram C shows betamethasone sodium phosphate USP standard 0.15 mg/mL solution at time 0 and Chromatogram D shows the same sample after degradation with heat (90°C) for 24 hours with 22.7% remaining. Betamethasone sodium phosphate degradation products eluted at 30.5 and 35 minutes.

Chromatogram E shows Celestone® Soluspan® packaged in polypropylene syringe on study day 0 and Chromatogram F shows the sample on study day 210.

CONCLUSIONS

Celestone® Soluspan® is physically and chemically stable for at least 210 days when stored at room temperature (15-30°C) with protection from light.

DISCLOSURES

Authors of this poster have the following to disclose concerning possible personal or financial relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Nathan H Ma – Nothing to disclose
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