Stability of Dexamethasone in Extemporaneously Prepared Oral Suspensions

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ABSTRACT

Objective: To evaluate the stability of 0.5 and 1.0 mg/mL dexamethasone suspensions in a vehicle consisting of equal parts of Ora-Sweet and Ora-Plus after storage at 4°C and 25°C for up to 91 days.

Methods: Suspensions of dexamethasone sodium phosphate 4 mg/mL injection solution in a 1:1 mixture of Ora-Sweet and Ora-Plus were prepared in 40-mL amber plastic bottles; final concentrations of dexamethasone were 0.5 and 1.0 mg/mL. Three bottles of each suspension were stored at 4°C (refrigerated), and 3 were stored at 25°C (room temperature). Physical characteristics, including pH, colour, odour, viscosity, precipitation, and ease of resuspension, were observed weekly for 91 days. Aliquots were removed from each bottle weekly for 91 days and stored at –84°C until analysis by a validated high-pressure liquid chromatography method. A suspension was considered stable if it maintained 90% of its initial concentration.

Results: No change in pH was observed in suspensions of either concentration after storage at 4°C or 25°C for 91 days. Changes in colour and odour were slight. Viscosity was constant. Precipitates were easily resuspended, and there was no caking or clumping of material. Suspensions of both concentrations of dexamethasone maintained at least 90% of initial concentration at both temperatures throughout the 91-day period.

Conclusions: Dexamethasone suspensions of both 0.5 and 1.0 mg/mL in a 1:1 mixture of Ora-Sweet and Ora-Plus were physically and chemically stable for a period of up to 91 days, with or without refrigeration. The expiry date for these products can therefore be set at 91 days.

Key words: dexamethasone, stability, suspension, high-performance liquid chromatography

RÉSUMÉ

Objectif : Évaluer la stabilité de suspensions de dexaméthasone à des concentrations de 0,5 et 1,0 mg/mL dans un excipient liquide composé à parts égales d'Ora Sweet et d'Ora Plus, après entreposage à 4 °C et 25 °C pendant une période allant jusqu'à 91 jours.

Méthodes : Les suspensions de phosphate sodique de dexaméthasone à raison de 4 mg/mL de solution pour injection dans un mélange 1:1 d'Ora-Sweet et d'Ora-Plus ont été préparées dans des flacons de plastique ambré de 40 mL; les concentrations finales de dexaméthasone étaient de 0,5 et 1,0 mg/mL. Trois flacons de chaque suspension ont été entreposés à 4 °C (au réfrigérateur) et trois autres à 25 °C (à la température ambiante). Les caractéristiques physiques, don le pH, la couleur, l'odeur, la viscosité, la précipitation et la facilité de remise en suspension ont été examinées à chaque semaine pendant les 91 jours. Les aliquotes ont été retirées de chaque flacon à toutes les semaines, pendant les 91 jours, et réfrigérées à –84 °C avant d'être analysées par une méthode validée de chromatographie liquide à haute pression. La suspension était considérée stable lorsqu'elle conservait 90 % de sa concentration initiale.

Résultats : Aucun changement du pH n'a été observé dans l'une ou l'autre des suspensions aux deux concentrations, après leur entreposage à 4 °C ou 25 °C pendant 91 jours. Une légère altération de la couleur et de l'odeur est cependant survenue. La viscosité était stable et les précipités ont été facilement remis en suspension, sans agglomération ni agglutination de la matière. Les suspensions des deux concentrations de dexaméthasone ont conservé au moins 90 % de leur concentration initiale aux deux températures pendant la période d'étude de 91 jours.

Conclusions : Les suspensions de dexaméthasone aux concentrations de 0,5 et 1 mg/mL dans un mélange 1:1 d'Ora Sweet et d'Ora Plus ont montré une stabilité physique et chimique pendant une période allant jusqu'à 91 jours, avec ou sans réfrigération. La date de péremption de ces produits peut par conséquent être établie à 91 jours.

Mots clés : dexaméthasone, stabilité, suspension, chromatographie liquide à haute pressions

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INTRODUCTION

Dexamethasone is an adrenal corticosteroid commonly used to treat endocrine and rheumatic disorders, as well as chemotherapy-induced nausea and vomiting.[1] At the authors' hospital, until the time of this study, dexamethasone was prepared as a suspension with the injection solution of the drug (Sabex Inc., Boucherville, Quebec), distilled water, and cherry flavouring syrup. The suspension was given an expiry date of 8 days for refrigerated storage. This short expiry date meant that hospital pharmacy staff had to prepare the suspension frequently and that discharged patients had to refill their prescriptions frequently, which led to relatively high expenditures of both money and time for both parties.

The suspension is an alternative dosage form for patients who are unable to swallow tablets or capsules. Ora-Sweet and Ora-Plus (Paddock Laboratories Inc., Minneapolis, Minnesota) are commercially available sweetening and suspending agents, respectively. A 1:1 mixture of these products used as a drug vehicle may ease product preparation and improve palatability. In Canada, the only commercially available liquid preparation of dexamethasone is dexamethasone elixir 0.1 mg/mL (Pharmascience Inc., Montreal, Quebec). In the United States, dexamethasone is available in several liquid formulations, including Decadron elixir 0.5 mg/5 mL (Merck & Co., Inc., Whitehouse Station, New Jersey), dexamethasone oral solution 0.5 mg/5 mL (Roxane Laboratories, Inc., Columbus, Ohio), and dexamethasone Intensol concentrate 0.5 mg/0.5 mL (Roxane Laboratories, Inc.).[2] However, the elixir and the concentrate contain 30% alcohol, which may be undesirable, particularly for children. Furthermore, the oral solution is available only in the 0.1 mg/mL strength. With such a low concentration (comparable to 0.5 mg/mL prednisone), 40 mL or more of the preparation is often needed for toddlers and preschool children.[3] The need for such a large volume leads to lower patient compliance and complicates the administration process for caregivers. For the above reasons, a palatable liquid formulation of dexamethasone with a concentration allowing reasonable administration volume is available only by extemporaneous preparation.

This study examined the physical characteristics and chemical stability (defined as maintenance of more than 90% of initial concentration) of extemporaneously prepared oral dexamethasone suspensions of 0.5 and 1.0 mg/mL in a 1:1 mixture of Ora-Sweet and Ora-Plus, stored at either 4°C or 25°C throughout a 91-day study period.

METHODS

Preparation of Suspension

Dexamethasone suspensions (0.5 and 1.0 mg/mL) were prepared in triplicate from commercially available dexamethasone phosphate injection solution 4 mg/mL (Sabex Inc., lot 101233) and a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories Inc., lots 8J6211 and 8J6233, respectively). Six replicates of each concentration were prepared in separate 40-mL amber plastic bottles, 3 of which were stored at 4°C (refrigerated) and 3 of which were stored at 25°C (room temperature). All bottles were exposed only to fluorescent light in the laboratory.

The physical appearance of the suspensions was evaluated qualitatively at the time of preparation and at weekly intervals up to 91 days. All suspensions were examined for changes in colour (against white and black backgrounds), odour, pH, and viscosity, and for formation of precipitates and ease of resuspension. All samples were allowed to equilibrate to room temperature before measurement of pH, and the pH meter (model 8000, VWR Canlab, Mississauga, Ontario) was calibrated at the beginning of each testing period. Immediately after the physical observations had been completed, each bottle was shaken manually for 10 s, and 0.8 mL of the suspension was removed and stored at –84°C until batch analysis by high-performance liquid chromatography (HPLC).

Preparation of Stock and Standards

Stock solutions of dexamethasone phosphate at 0.25, 0.50, 0.75, 1.00, and 1.50 mg/mL were prepared by diluting dexamethasone phosphate injection solution (4 mg/mL) in saline (0.9% sodium chloride injection USP, Baxter Corp., Toronto, Ontario, lot W9C17B1). The internal standard was methylprednisolone 1.0 mg/mL (Sigma Aldrich, Oakville, Ontario, lot 97H0355) in HPLC-grade methanol (Fisher Scientific, Richmond, British Columbia, lot 001327). Standard solutions were prepared by combining a 0.05-mL aliquot of each stock solution and a 0.05-mL aliquot of methylprednisolone 1.0 mg/mL and further diluting with HPLC-grade methanol to make up 1.0-mL volumes. The final concentration of dexamethasone in the samples injected onto the chromatograph were 0.0125, 0.0250, 0.0375, 0.0500, and 0.0750 mg/mL. Before injection, all standard solutions were passed through a 0.45-µm microfilter (Acrodisc GHP syringe

filter, Gelman, Ann Arbor, Michigan, lot 5874), to prevent injection of impurities onto the column.

The HPLC instrumentation (model 2690, Waters Alliance Systems, Waters Ltd., Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200-µL injector, a Nova-Pak 3.9 x 20 mm guard column (Waters Ltd., lot W93131), a Nova-Pak C18 3.9 x 150 mm column (Waters Ltd., lot W83351M158), and an ultraviolet detector set at 238 nm (model 2487 dual-wavelength absorbance detector, Waters Ltd.). The mobile phase was developed in the authors' laboratory and consisted of a 25:10:32.5:32.5 (v/v) mixture of water (Fisher Scientific, lot 003433), methanol (Fisher Scientific, lot 001327), acetonitrile (Fisher Scientific, lot 990699), and 0.04 mol/L sodium phosphate buffer (Sigma Aldrich, lot 89H0030; pH 7.5). All solvents were HPLC grade and had been filtered before use. The flow rate was set at 1 mL/min.

A 5-point calibration curve was prepared, with a blank (methanol only) at the beginning of each run, to ensure that there was no carry-over from one run to the next. The range of this calibration curve (0.25 to 1.50 mg/mL before dilution) encompassed the diluted test concentrations of 0.5 mg/mL and 1.0 mg/mL. The calibration curve was generated by least-squares regression of the peak area ratio of dexamethasone to methylprednisolone and the concentration of each standard solution. Determinations of accuracy were based on the deviation of measured from nominal (i.e., "known") concentrations of the standard curves over 4 days. The precision of the assay was evaluated by intra-day and inter-day validation methods. Intra-day variation was determined by running 0.25, 0.50, and 1.50 mg/mL stock solutions (diluted to standards of 0.0125, 0.025, and 0.075 mg/mL) in quadruplicate throughout a single day, whereas inter-day variation was determined by running the same concentrations (as in the testing for intra-day variation) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation were then calculated. Acceptable limits for the coefficients of variation were defined a priori as less than 10%.

Degradation of Dexamethasone

Dexamethasone phosphate injection solution (4 mg/mL) was diluted in saline to a concentration of 1.5 mg/mL, and the diluted sample was acidified with concentrated hydrochloric acid (Fisher Scientific, lot 299067) to a pH of 1.86. This solution was incubated in a 90°C water bath for 2 h and then boiled for 5 min. The chromatogram obtained for the degraded solution was compared with a chromatogram obtained from a standard solution (1.5 mg/mL) to determine any changes in concentration, retention time, and peak shape.

Preparation of Samples

Dexamethasone study samples were processed in a manner similar to that for the stock solutions. For each study sample (both concentrations, both temperatures, in triplicate), a 0.05-mL aliquot was diluted with 0.9 mL HPLC-grade methanol, and a 0.05-mL aliquot of methylprednisolone 1 mg/mL in HPLC-grade methanol was added. The final theoretical concentrations were 0.025 and 0.050 mg/mL, respectively. Each solution was passed through a 0.45-µm microfilter before a 40-µL sample was withdrawn and injected onto the column.

Statistical Analysis

The means, standard deviations, and coefficients of variation were calculated for samples analyzed in triplicate and quadruplicate. For each study day the percentage of the initial dexamethasone concentration remaining was calculated for each sample. The percentage of dexamethasone remaining on day 91 was calculated from the concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero x 100. The 95% confidence interval (CI) of the amount remaining on the last study day was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of the 95% CI of the concentration on day 91/concentration on day zero x 100. Stability was defined as maintenance of at least 90% of the initial dexamethasone concentration.

RESULTS

Regression analysis of the peak area ratio of dexamethasone to internal standard versus concentration demonstrated linearity over the working range of concentrations, with coefficients of determination (r^2) greater than 0.992 (n = 5). Determinations of accuracy showed less than 1.15% deviation from theoretical concentrations. The intra-day (n = 4) and inter-day (n = 4) coefficients of variation for the 3 different concentrations were within acceptable limits: 1.53% and

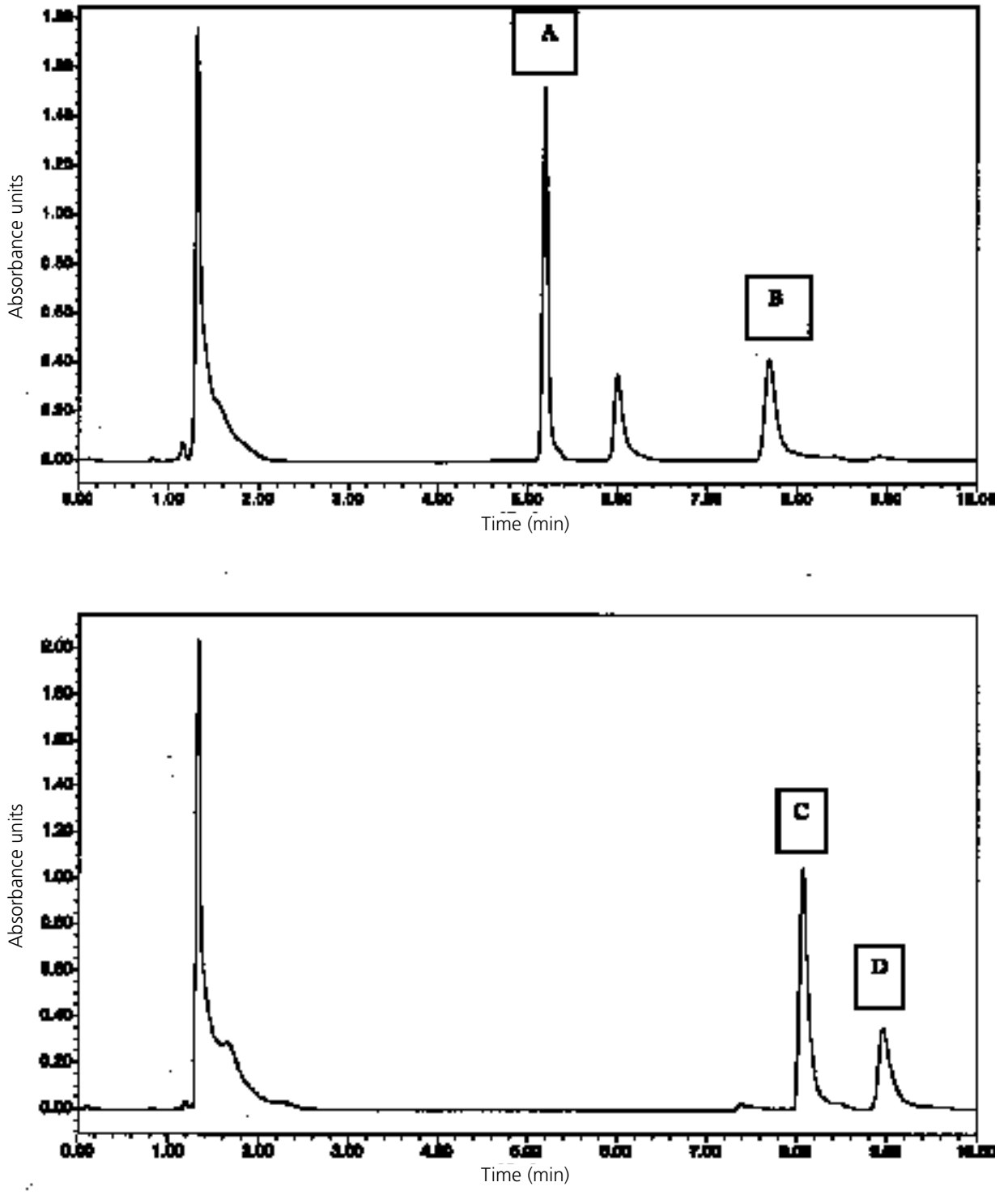

Figure 1. Upper panel: Representative chromatogram showing the dexamethasone peak (A) at 5.2 min and the methylprednisolone peak (B) at 7.7 min. Lower panel: Chromatogram depicting the degradation study with dexamethasone degradation products (C and D) at 8.1 and 8.9 min, respectively.

Table 1. Mean Dexamethasone Concentration ± Standard Deviation (and Mean Percentage Remaining*) during 91 Days of Storage at 4°C and 25°C

	0.5 mg/mL†				1.0 mg/mL†			
Study Day	4°C		25°C		4°C		25°C	
0	0.480±0.070		0.469±0.083		1.022±0.112		0.994±0.020	
7	0.499±0.087	(103.96)	0.495±0.039	(105.54)	1.091±0.051	(106.75)	0.980±0.064	(98.59)
14	0.482±0.061	(100.42)	0.490±0.012	(104.48)	1.049±0.087	(102.64)	1.027±0.070	(103.32)
21	0.451±0.055	(93.96)	0.466±0.021	(99.36)	0.932±0.026	(91.19)	0.920±0.084	(92.56)
28	0.432±0.008	(90.00)	0.445±0.035	(94.88)	0.972±0.112	(95.11)	0.928±0.011	(93.36)
35	0.468±0.026	(97.50)	0.471±0.031	(100.43)	1.072±0.104	(104.89)	0.934±0.084	(93.96)
42	0.519±0.064	(108.13)	0.493±0.031	(105.12)	1.071±0.046	(104.79)	1.015±0.065	(102.11)
49	0.488±0.025	(101.67)	0.450±0.053	(95.95)	1.092±0.060	(106.85)	1.044±0.020	(105.03)
56	0.471±0.012	(98.13)	0.478±0.042	(101.92)	1.002±0.024	(98.04)	1.028±0.045	(103.42)
63	0.455±0.047	(94.79)	0.499±0.027	(106.40)	1.065±0.139	(104.21)	0.987±0.084	(99.30)
70	0.472±0.152	(98.33)	0.488±0.085	(104.05)	1.002±0.078	(98.04)	0.979±0.119	(98.49)
77	0.523±0.012	(108.96)	0.453±0.041	(96.59)	1.058±0.031	(103.52)	1.091±0.024	(109.76)
84	0.500±0.043	(104.17)	0.491±0.062	(104.69)	1.037±0.038	(101.47)	1.080±0.028	(108.65)
91	0.480±0.031	(100.00)	0.488±0.076	(104.05)	0.975±0.049	(95.40)	0.948±0.057	(95.37)
% remaining on day 91 by linear regression‡	96.31		98.34		101.00		93.97	
Lower limit of 95% CI for % remaining§	92.29		96.38		95.01		91.45	

CI = confidence interval.
*Percentage remaining was calculated in relation to the initial concentration (day zero).
†Nominal concentration.
‡Calculated from concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/ concentration on day zero x 100.
§Calculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% CI of concentration on day 91/concentration on day zero x 100.

3.95%, respectively, for the 0.25 mg/mL solution; 1.96% and 7.33%, respectively, for the 0.50 mg/mL solution: and 1.14% and 1.57%, respectively, for the 1.50 mg/mL solution.

When the dexamethasone was subjected to degradation, a major degradation product eluted at 8.1 min and a minor one at 8.9 min (Figure 1). Neither of these products interfered with the quantification of the parent dexamethasone compound or the methylprednisolone internal standard. Thus, the HPLC method was deemed capable of indicating stability.

No significant changes in physical appearance or odour of the suspensions were observed throughout the 91 days. Each cloudy white suspension had a faint sweet smell, maintained the same viscosity, and was easily resuspended throughout the study period. Furthermore, no fluctuations in pH were observed. The mean pH (± standard deviation) was 5.18 ± 0.07 for the 0.5 mg/mL suspension stored at 4°C, 5.09 ± 0.04 for the 0.5 mg/mL suspension stored at 25°C, 5.63 ± 0.06 for the 1.0 mg/mL suspension stored at 4°C, and 5.56 ± 0.05 for the 1.0 mg/mL suspension stored at 25°C.

The retention time for dexamethasone was 5.2 min, whereas the retention time for the internal standard methylprednisolone was 7.7 min (Figure 1). The HPLC analysis showed that, at both storage temperatures, the 0.5 and 1.0 mg/mL suspensions maintained at least 90% of their initial concentrations on every study day (Table 1). Furthermore, about 94% of the initial dexamethasone concentration remained on day 91, according to linear regression analysis of the concentration-time data, and the lower limit of the 95% confidence interval indicated that more than 91% of the initial concentration remained on day 91 (Table 1).

DISCUSSION

Until the time of this study, dexamethasone suspension had been prepared at the authors' institution from 4 mg/mL dexamethasone phosphate injection solution, distilled water, and cherry flavouring. This product had an expiry date of 8 days when kept refrigerated. The advantage of the injection solution is

that the drug is already dissolved, which eliminates the need for grinding or crushing, as would be required with tablets. This in turn prevents potential physical instability and microbial contamination. Hence, all suspensions used in this study were prepared from the injection solution.

A few liquid formulations of dexamethasone are available on the US market and one liquid product is available in Canada, but either they contain alcohol or their strength is lower than desirable. Hence, these commercially available products have the potential to increase adverse effects and noncompliance, particularly among children.

To the authors' knowledge, there are no published stability studies on dexamethasone suspension prepared in a 1:1 mixture of Ora-Sweet and Ora-Plus. A MEDLINE search (1966 to 2000) with the terms "dexamethasone", "stability", and "HPLC" yielded 12 articles, of which 7 were relevant. These articles evaluated the stability of dexamethasone in intravenous solutions either by itself[4] or mixed with other drugs.[5-10] None evaluated the stability of dexamethasone in extemporaneously compounded suspensions. However, information regarding the 60-day stability of dexamethasone phosphate 1 mg/mL in wild cherry flavoured oral syrup is available from the Hospital for Sick Children Web site.[11]

In the weekly analysis, colour and odour changes were slight, and samples were easily resuspended without caking, clumping, or crystal formation. Although these measures are qualitative, observations were documented by the same person throughout the 91 days, which eliminated inter-personnel bias. Variation in pH was not notable; pH ranged from 5.0 to 5.3 in the 0.5 mg/mL samples and from 5.4 to 5.7 in the 1.0 mg/mL samples.

A limitation of this study design relates to the freezing of samples at –86°C until the time of batch analysis. It was assumed that dexamethasone would not degrade at this low temperature and that no volume losses would occur because of freeze-drying during storage. In addition, it was assumed that errors due to serial analysis would have been greater than any errors occurring with batch analysis.

According to qualitative and HPLC analyses of weekly samples, dexamethasone suspensions of 0.5 and 1.0 mg/mL stored at either 4°C and 25°C remained stable and maintained at least 90% of their original concentrations for up to 91 days. These results led to changes at the authors' hospital for extemporaneous compounding of dexamethasone suspensions, and the expiry date has been extended from 8 days to 3 months.

References

1. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 9th ed. New York (NY): McGraw-Hill; 1996. p. 931.
2. Dexamethasone. In: *American Hospital Formulary Service drug information*. Bethesda (MD): American Society of Health-System Pharmacists; 2000. p. 2756.
3. Weinberger M. Corticosteroids for exacerbations of asthma: problems and solutions. *J Pediatr* 2000;136:276-8.
4. Lugo RA, Nahata MC. Stability of diluted dexamethasone sodium phosphate injection at two temperatures. *Ann Pharmacother* 1994;28:1018-9.
5. Vermeire A, Remon JP. Compatibility and stability of ternary admixtures of morphine with haloperidol or midazolam and dexamethasone or methylprednisolone. *Int J Pharm* 1999;177:53-67.
6. Chin A, Moon YS, Chung KC, Gill MA. Stability of granisetron hydrochloride with dexamethasone sodium phosphate for 14 days. *Am J Health Syst Pharm* 1996;53:1174-6.
7. Mayron D, Gennaro AR. Stability and compatibility of granisetron hydrochloride in i.v. solutions and oral liquids and during simulated Y-site injection with selected drugs. *Am J Health Syst Pharm* 1996;53:294-304.
8. Allen LV Jr, Stiles ML, Prince SJ, Sylvestri MF. Stability of cefpirome sulfate in the presence of commonly used intensive care drugs during simulated Y-site injection. *Am J Health Syst Pharm* 1995;52:2427-33.
9. Stiles ML, Allen LV Jr, Prince SJ, Holland JS. Stability of dexamethasone sodium phosphate, diphenhydramine hydrochloride, lorazepam, and metoclopromide hydrochloride in portable infusion-pump reservoirs. *Am J Hosp Pharm* 1994;51:514-7.
10. Walker SE, DeAngelis C, Iazzetta J, Eppel JG. Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991;48:2161-6.
11. Hospital for Sick Children. Dexamethasone phosphate 1 mg/mL oral syrup. Available at: http://www.sickkids.on.ca/pharmacy/dexameth.asp [accessed 2000 Dec 1].

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