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Journal of Pharmaceutical and Biomedical Analysis 38 (2005) 332–336
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Shelf lives of aseptically prepared medicines – stability of hydrocortisone sodium succinate in PVC and non-PVC bags and in polypropylene syringes

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Received 18 July 2004; received in revised form 17 December 2004; accepted 20 December 2004
Available online 8 February 2005

Abstract

Parenteral aseptic preparations of hydrocortisone sodium succinate (HSS) are used frequently in hospitals, but little definitive stability information is available. The purpose of this study was to obtain ultimate shelf lives for typical formulations so that they may be prepared in bulk in appropriately licensed facilities.

In the first study, the stability of HSS, 1 mg/ml, was determined in polyvinyl chloride (PVC) bags and polyolefine (non-PVC) bags, in 0.9% (w/v) sodium chloride at 7 °C, 25 °C/60% relative humidity (RH) and room temperature in the light (RTL) with storage for up to 135 days. In the second study, the stability of HSS, 50 mg/ml was determined in polypropylene syringes at 5 °C and 25 °C/60% RH with storage for up to 120 days.

Samples from each admixture were analysed by stability indicating high performance liquid chromatography (HPLC) and were monitored for pH, appearance of solution and container, and the rate of appearance of decomposition products.

Shelf lives were calculated using the maximum rate method. HSS at a concentration of 1 mg/ml in PVC bags was stable for up to 41 days at 7 °C, 8 days at 25 °C and 7 days at RTL. It was stable in non-PVC bags for up to 48, 8 and 6 days, respectively. HSS in polypropylene syringes at a strength of 50 mg/ml was stable for up to 81 days at 5 °C and 6 days at 25 °C.

Keywords: Hydrocortisone; Hydrocortisone sodium succinate; Solu-Cortef; Stability; Shelf life

1. Introduction

Hydrocortisone is a synthetic corticosteroid administered when the body is deficient in the natural hormone. It is used in the treatment of inflammation, allergy, collagen diseases, asthma, adrenocortical deficiency, shock and some neoplastic conditions.

Hydrocortisone is heat labile and must not be autoclaved, [1] therefore, it needs to be prepared aseptically.

Hydrocortisone sodium succinate (HSS) is the sodium salt of an ester of hydrocortisone. It is more soluble in aqueous solution than hydrocortisone and is widely used in aseptic formulations. Solubilisation is achieved through the use of the ionisable succinate moiety, which is cleaved in vivo to release the active parent compound, hydrocortisone.

For the practice of preparing these dosage forms in properly controlled aseptic facilities to be viable, large batch production needs to be adopted, which in turn relies on a long shelf life of the product being available.

There is limited published information on the stability of HSS in aseptic preparations. Gupta and Ling [2] reported that HSS 10 mg/ml in 0.9% (w/v) sodium chloride stored in polypropylene syringes lost less than 10% after 7 days at 25 °C and less than 3% after 21 days at 5 °C. Cradock, Kleinman and Rahman [3] showed that HSS 1 mg/ml in 0.9% sodium chloride exhibited no decomposition (by UV spectroscopy) in 24 h at room temperature in the light or at 30 °C,

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doi:10.1016/j.jpba.2004.12.026

but in 7 days 10% decomposition at room temperature and 15% at 30 °C was observed.

There was a need for a more prolonged and detailed study to allocate a validated shelf life.

2. Experimental

2.1. Materials and reagents

All commercial reagents and materials were obtained from VWR International Ltd. (Lutterworth, England). Hydrocortisone sodium succinate injection (Solu-Cortef®) was obtained from Pharmacia Ltd. (Milton Keynes, England). Hydrocortisone was purchased from Sigma-Aldrich Company Ltd. (Poole, England). Polyvinyl chloride (PVC) 100 ml bags containing 0.9% (w/v) sodium chloride were kindly supplied by Baxter Healthcare Ltd. (Thetford, England). Polyolefine (Non-PVC) 100 ml Freeflex® bags containing 0.9% (w/v) sodium chloride were kindly supplied by Fresenius Kabi Ltd. (Runcorn, England). Polypropylene 2 ml Omnifix® syringes were obtained from B|Braun Ltd. (Sheffield, England). Luerlock syringe caps were obtained from Baxa Ltd. (North Ascot, England).

2.2. Apparatus and chromatographic conditions

The high performance liquid chromatographic (HPLC) system (Thermo Electron, Hemel Hempstead, England) consisted of a vacuum degasser, binary gradient pump (P200), autosampler fitted with automated sample preparation facilities (AS3000) and a UV–Vis detector (UV150). Chromatographic results were collected by data handling software (Scientific Software Inc. EzChrom Elite Ver 2.61, Aston Scientific Ltd., Stoke Mandeville, England). Measurements of pH were carried out using a combination electrode pH meter (Corning, model 120, Halstead, England).

The chromatographic separation was performed at ambient temperature on a reversed phase Lichrospher C_{18} column 150 × 4.6 mm i.d., 5 μm particle size (Phenomenex Macclesfield, England). Elution was established with a mobile phase composition of phosphate buffer pH 7 0.1 M mixed BP and methanol (50:50 v/v) at a flow rate of 1.2 ml/min. The chromatographic signal was monitored at 254 nm. The injection volume was 10 μl.

2.3. Standard and sample solutions for HPLC analysis

Stock solutions of HSS in water at a nominal concentration of 1 mg/ml as hydrocortisone free base were further diluted with water to give a final injection concentration of 0.1 mg/ml. Two independent standards were used at each time point.

Samples were diluted in water to give a nominal injection concentration of 0.1 mg/ml, in line with the standard.

The second dilutions were carried out using the autodilution function of the autosampler in all cases.

2.4. Preparation of admixtures

A HSS vial (Solu-Cortef®, 100 mg) was reconstituted with 2 ml of water. This was added to a 100 ml bag containing 0.9% (w/v) sodium chloride to give a nominal concentration of 1 mg/ml of hydrocortisone.

The syringes were prepared by weighing an amount of HSS equivalent to 50 mg/ml of hydrocortisone in water for injection. This solution was distributed into 2 ml syringes and capped.

2.5. Stability study protocol

Two PVC and two non-PVC bags were stored at each of 7 ± 1 °C, 25 ± 2 °C and 60 ± 5% relative humidity (RH) and at room temperature in the light (RTL). 7 °C was chosen to reflect the highest temperature the bags were likely to be exposed to in a hospital refrigerator conforming to the ICH standard condition for refrigerated storage [4]. 25 °C/60% RH is the ICH guideline condition for long term stability testing and is representative of room temperature storage. RTL (room temperature exposed to continuous irradiation from daylight fluorescent tubes) was chosen to reflect the conditions that the bags may be exposed to on a hospital ward.

Eighteen polypropylene syringes were stored at 5 °C (The refrigerator used to store the syringes was lower in temperature than the expected 7 °C) and 14 at 25 °C/60% RH. At each time point, two syringes and duplicate samples from each bag were tested. The pH, HSS content, appearance of decomposition products and appearance of solution and container were monitored. A sterility test [5] was carried out at initial and final time points, on extra bags prepared aseptically, especially for this purpose.

2.6. Calculation of shelf life

The shelf life was calculated using the confidence bound method or maximum rate method [6].

The slope of the regression line of ln (concentration) versus time represents the rate constant (k) of the decomposition. The regression line was constructed using all the individual assay values.

The maximum rate method calculates the upper confidence bound of this rate of decomposition, which thus corresponds to the maximum rate of decomposition represented by the analytical data.

A validated Excel™ spreadsheet was used to calculate the shelf lives based on an acceptable loss of 10% of the initial concentration (t_{90}).

3. Results

3.1. Assay validation

Three peaks were observed in sample and standard chromatograms (Fig. 1). HSS eluted at 7.1 min. The peak observed

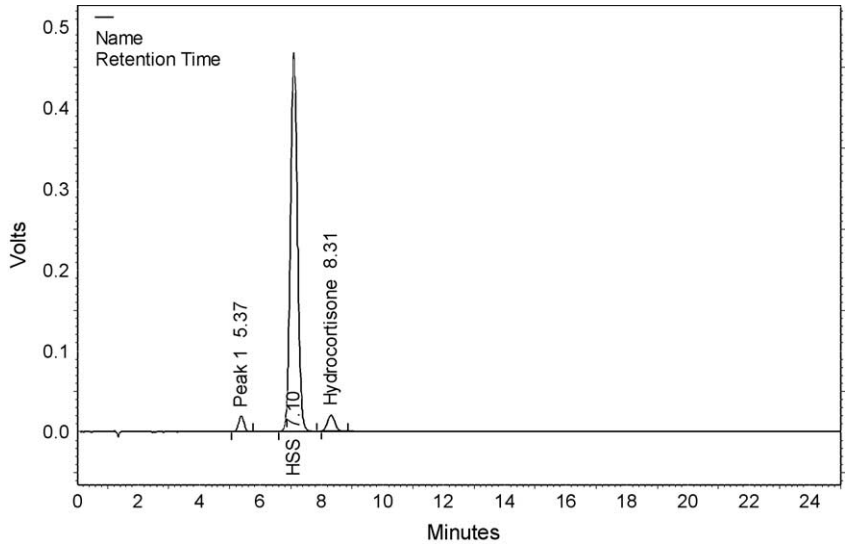

Fig. 1. Typical chromatogram of hydrocortisone sodium succinate sample/standard.

at 8.3 min was tentatively identified as free hydrocortisone by the identical retention time obtained by injection of pure hydrocortisone in solution. The peak at 5.4 min was unknown. All peaks were base line separated (resolutions greater than 1).

Selectivity experiments were carried out, in order to determine whether the proposed method could separate HSS degradation products or impurities. Accelerated decomposition on heating aqueous solutions of HSS at 60 °C for a period of up to 12 days showed a decrease in HSS peak area with accompanying increases in hydrocortisone and unknown peak 1 areas. On further heating, a slight fall in unknown peak1 was noted. No other peaks were present.

A mass balance calculation was carried out. The analysis of a sample stored at 25 °C/60% RH for 29 days demonstrated a composition of 70% HSS and 15.6% H, thus implying a conversion to unknown 1 of 14.4%. Based on peak area, the proportion of the total represented by unknown 1 was 15%. This confirms that all the components of the sample were eluted and reported in the chromatographic run.

The only known reported significant degradation pathway of HSS is hydrolysis to yield hydrocortisone and succinic acid. [7] It can be seen from the accelerated decomposition that HSS does decompose to hydrocortisone. However, Unknown peak 1 is not succinic acid.

An attempt was made to isolate and identify unknown peak 1. A volatile eluant system consisting of methanol–water (50:50, v/v) gave analogous separation of the three peaks as the analytical method but with poor peak shape. The eluant was collected at the retention time of unknown peak 1, and evaporated to dryness. On re-dissolving in methanol: water and re-chromatographing it was noted that not only unknown peak 1 was observed but also HSS. Collection and evaporation were repeated twice more in order to rule out any unintentional collection of HSS. HSS was still observed.

Anderson and Taphouse [8], reported studies of acyl migration in methylprednisolone 21-sodium succinate and 17-succinate. They observed three peaks in the HPLC of methylprednisolone-21-succinate, identified unambiguously as methylprednisolone-21-succinate, free methyl prednisolone and methyl prednisolone-17-succinate. They concluded that reversible acyl migration is the dominating reaction at pH 3.6–7.4. An authentic sample of methylprednisolone sodium succinate chromatographed in on our HPLC system showed three peaks. The most retained peak was tentatively identified as methylprednisolone by retention time comparison with the authentic material.

This conclusion strongly supports our findings and it is postulated that due to the similar structure of methyl prednisolone-21-succinate and hydrocortisone-21-succinate that unknown peak 1 is in fact hydrocortisone-17-succinate. This possible acyl migration reaction is shown in Fig. 2.

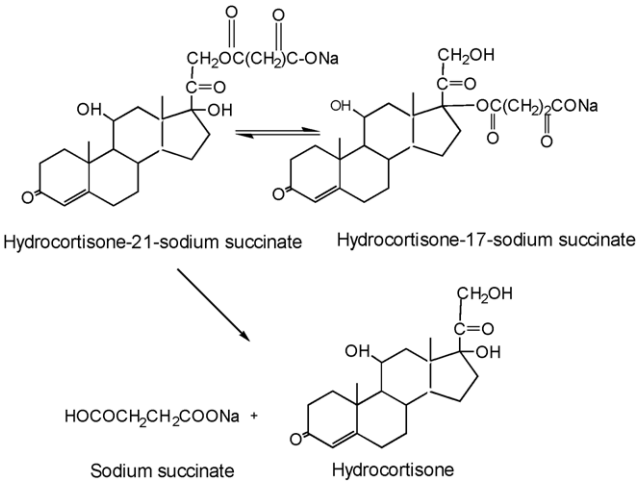

Fig. 2. The aqueous solvolysis of hydrocortisone sodium succinate.

Table 1
Results of bag studies

Time (days)	PVC bags % of initial HSS remaining			Non-PVC bags % of initial HSS remaining		
	7 °C	25 °C	RTL	7 °C	5 °C	RTL
0	100.0	100.0	100.0	100.0	100.0	100.0
1	101.3	94.8	–	96.8	–	–
2	–	96.6	–	99.7	–	–
3	99.5	89.5	–	–	–	–
4	–	88.9	–	–	–	–
6	98.3	–	–	98.5	–	–
7	100.3	85.6	–	96.2	–	–
8	–	–	81.6	–	75.3	77.1
9	–	79.2	–	–	–	–
12	–	–	80.0	–	75.3	77.9
14	93.0	–	–	–	70.3	–
15	93.8	–	–	92.0	–	–
16	–	77.8	78.0	–	73.5	73.1
19	–	–	71.7	–	70.6	66.8
22	–	74.0	–	–	–	–
23	–	–	71.9	–	69.7	67.7
29	–	70.0	65.8	–	–	–
30	87.5	–	–	88.0	–	–
36	–	–	–	–	64.1	60.5
63	–	–	–	84.9	–	–
68	80.4	–	–	–	–	–
90				80.6	–	–
104	77.6	–	–	–	–	–
131	–	–	–	77.0	–	–
135	74.6	–	–	–	–	–

3.2. Precision, accuracy, recovery and linearity

The method precision (repeatability of sample) was established by assaying six replicates of sample. Intermediate precision measurement was carried out on a different instrument, different HPLC column and on a different day. The overall precision was 0.80% R.S.D. ($n = 12$).

The accuracy of the assay system was assessed by spiking a sample with 20, 50, 75, 100 and 125% of the label claim with HSS. The average recovery at the 100% level was 101.8%, calculated from the equation:

$$\left[\frac{\text{Actual amount found (mg/ml)}}{\text{Theoretical amount (mg/ml)}}\right] \times 100$$

The linear regression analysis of the dependence of the amount found in mg/ml (y) on the amount added in mg/ml (x) in the accuracy determination gave the equation $y = 0.9982x + 2.9372$, with a correlation coefficient of 0.9996.

3.3. Results of stability study

3.3.1. PVC and non-PVC bags

The rate of decomposition at 25 °C /60% RH and at RTL was essentially the same for both bag types. Non-PVC bags at 7 °C showed a slightly slower rate of decomposition than the PVC bags. (Tables 1 and 2).

pH changes were greater at 25 °C/60% RH (7.3–6.3) and RTL (7.2–6.4) after 30 days storage than at 7 °C (7.2–6.4) after 135 days storage. No difference in pH was observed between the different types of bags.

No change was observed in the colour and appearance of the solutions or the bags. All samples showed an increase in the areas of the hydrocortisone and unknown 1 peaks as the hydrocortisone sodium succinate peak area decreased. The bag contents were sterile at all time points.

3.3.2. Polypropylene syringes

The rate of decomposition was faster at 25 °C/60% RH than at 5 °C (Tables 3 and 4). pH changes were greater at 25 °C/60% RH (pH 7.6–6.9 after 29 days) than at 5 °C (pH

Table 2
Rate constants for bag studies

	PVC bags			Non-PVC bags		
	7 °C	25 °C	RTL	7 °C	25 °C	RTL
Rate constant, k (day^{-1})	-2.32×10^{-3}	-1.12×10^{-2}	-1.34×10^{-2}	-2.00×10^{-3}	-1.05×10^{-2}	-1.30×10^{-2}
Calculated shelf life (days)	41.3	8.4	6.9	48.2	8.0	6.9

Table 3
Results of syringe study

Time (days)	% of initial HSS remaining	
	5 °C	25 °C
0	100.0	100.0
2	99.9	–
4	98.4	–
7	104.8	–
8	–	96.5
12	–	92.9
15	97.0	91.0
16	–	85.4
19	–	80.9
23	–	75.7
29	–	70.5
31	90.8	–
62	95.5	–
120	91.2	–

Table 4
Rate constants for syringe study

	5 °C	25 °C
Rate constant, k (days^{-1})	-8.20×10^{-4}	-1.31×10^{-2}
Calculated shelf life (days)	81.2	6.8

7.6–6.3 after 130 days). No change was observed in the colour and appearance of the solution or the syringe at either temperature.

4. Discussion

Both bag types stored at 7 °C, 25 °C/60% RH and RTL showed similar rate constants, PVC bags had a marginally higher rate, which could be due to sorption of HSS by the polyvinyl chloride.

Both PVC and non-PVC bags stored at RTL showed marginally higher rates than at other temperatures suggesting that decomposition could be accelerated by light.

Syringes containing 50 mg/ml HSS stored at 5 °C were much more stable than bags containing 1 mg/ml HSS at 7 °C.

5. Conclusion

Hydrocortisone sodium succinate in 0.9% (w/v) sodium chloride at a strength equivalent to 1mg/ml hydrocortisone was stable for up to 8 days when stored in PVC or non-PVC bags at 25 °C/60% RH.

It was stable for up to 7 days when stored in PVC and up to 6 days when stored in non-PVC at RTL, however, it should be protected from light where possible.

It was stable for up to 41 days when stored in PVC bags and up to 48 days when stored in non-PVC bags at 7 °C.

Hydrocortisone sodium succinate in water for injection at a strength equivalent to 50 mg/ml hydrocortisone in polypropylene syringes was stable for up to 6 days at 25 °C/60% RH and up to 81 days at 5 °C.

Acknowledgements

The authors wish to acknowledge the kind donation of PVC bags from Baxter Healthcare Ltd. and Non-PVC bags from Fresenius Kabi Ltd. We also thank the NHS Executive, North West R&D Directorate for the grant which made the study possible.

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