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Scientific paper

Evaluation of the Stability of Hydrocortisone Sodium Succinate in Solutions for Parenteral Use by a Validated HPLC-UV Method

Katja Mihovec,[1] Žane Temova Rakuša,[2] Enikő Éva Gaál[2] and Robert Roškar[2]

[1] *University Medical Centre Ljubljana, Slovenia*

[2] *University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia*

* *Corresponding author: E-mail: robert.roskar@ffa.uni-lj.si*
Tel: +386 1 4769 655

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Abstract

This study aimed to determine the in-use stability ($t_{95\%}$) of hydrocortisone sodium succinate (HSS) infusion solutions and provide evidence-based guidelines on their usability.

HSS infusion solutions were prepared and stored as recommended by the manufacturer and under common conditions in our hospital. The effects of HSS concentration (1 and 4 mg/mL), solvent (isotonic saline and glucose), temperature (ambient and 30 °C), and light on its stability were evaluated using a validated stability-indicating HPLC-UV method.

HSS degradation followed first-order kinetics. No significant difference in its stability was observed between the two evaluated concentrations, solvents and light exposure ($t_{95\%}$ between 25 and 30 h). Elevated temperature (30 °C) affected HSS stability and significantly reduced the $t_{95\%}$ (4.6–6.3 h).

HSS infusion solutions are physically and chemically stable (<5% degradation) for at least 6 h if stored below 30 °C. The in-use stability may be extended up to 24 h if stored below 24 °C.

Keywords: Forced degradation study; in-use stability; infusion; injection; Solu-Cortef.

1. Introduction

Cortisone is a glucocorticoid hormone synthesized endogenously in the adrenal gland cortex, as a response to stress.[1] Its synthetic form – hydrocortisone, mostly as hydrocortisone sodium succinate (HSS), is used in medicines for various conditions, requiring rapid and intense corticosteroid effects, such as acute or chronic adrenal insufficiency, various autoimmune and allergic diseases, and septic shock, unresponsive to fluid resuscitation and treatment with vasopressors.[2,3] Thus, the use of HSS as a continuous infusion is associated with more stable cortisol plasma concentrations and reduced fluctuation in blood glucose levels compared to intermittent boluses.[4] This is particularly important in patients with diabetes, as hyperglycaemia is one of the most common glucocorticoid side effects.[4,5] The application of continuous HSS infusion is also well-established practice for critically ill patients in hospital intensive care units (ICUs), also including the ICU of our hospital. For such purposes, commercially available medicinal products, in the form of vials containing freeze-dried powder for solution for injection/infusion, are used. Thus, an intravenous infusion is prepared as recommended by the manufacturer – by reconstituting the powder with 2 mL of sterile water for injection and addition of this solution to 100–1000 mL of 5% glucose in water or isotonic saline solution or 5% glucose in isotonic saline solution under aseptic conditions.[2] While the manufacturer recommends immediate use after reconstitution with sterile water for injection and disposal of any remainder, no information is provided on the in-use stability of the diluted HSS solution for infusion.[2] HSS is an ester, susceptible to hydrolysis and other degradation reactions (oxidation and transesterification) in aqueous solutions.[6–8] In a broader sense, data on HSS stability can be found in the literature, as HSS stability studies in oral solutions and suspensions,[9,10] solutions for infusion,[11,12] or as compatibility studies with other drugs.[13–15] Focusing on stability studies of HSS individually in solutions for infusion, which are limited to isotonic saline solutions, we identified a need for

a stability study under clinically relevant real-life conditions, since the type of media, temperature, and HSS concentration may affect its stability.[8–10] As medical personnel deal with these issues on daily basis, our primary objective within this study was to evaluate the stability of HSS under common real-life conditions and thus provide evidence-based guidelines. For such purpose, we investigated the stability of HSS in solutions for infusion, as commonly prepared in our hospital, by using a stability-indicating HPLC-UV method. We thus evaluated the effect of clinically relevant HSS concentration (1 mg/mL and 4 mg/mL), type of reconstitution solvent (isotonic saline and glucose solutions), temperature (24 °C and 30 °C), and light (protected and exposed to daylight) on its stability in infusion solutions.

2. Experimental

2. 1. Chemicals and Preparations

HPLC grade acetonitrile (ACN) was purchased from Sigma-Aldrich (Steinheim, Germany). Hydrochloric acid (HCl) and sodium hydroxide (NaOH) solutions (Titrisol®) as well as phosphoric acid (H_3PO_4) (85%) were purchased from Merck (Darmstadt, Germany). H_2O_2 solution (30%) was purchased from Honeywell Fluka™ (Seelze, Germany). High purity water was obtained using a Milli-Q A10 Advantage water purification system (Millipore Corporation, Bedford, MA, USA). Solu-Cortef 100 mg powder for solution for injection or infusion (Pfizer, Luxembourg, Luxembourg), and solutions for infusion: 0.9% sodium chloride (S) in 50 mL infusion bags (Baxter, Deerfield, Illinois, USA), and 5% glucose (G) in 100 mL intravenous (IV) containers (B. Braun, Melsungen, Germany) were used. Due to the lack of an HSS reference standard, its calibration and quality control (QC) solutions, as well as samples for the forced degradation study, were prepared by dissolving a portion of the powder of the medicinal product Solu-Cortef in Milli-Q water. The total powder was initially weighted to calculate the share of HSS, according to the reported HSS content in the product.

2. 2. Instrumentation and Chromatographic Conditions

The analysis was performed on an Agilent 1100/1200 series HPLC system (Agilent Technologies, Santa Clara, CA, USA) equipped with a UV–VIS detector and a ChemStation data acquisition system. A reversed-phase Luna C18 250 × 4.6 mm, 5 μm particle size column (Phenomenex, Torrance, CA, USA) at 40 °C using 1% (v/v) H_3PO_4 (mobile phase A), and ACN (mobile phase B) in isocratic mode (33% A, 67% B), at a flow-rate of 1.5 mL/min was utilized for the analysis. Detection was performed at 254 nm. The injection volume was 2 μL. The retention time (t_r) of HSS was 10.8 min and the total runtime was 13 min.

2. 3. Preparation of Samples for Forced Degradation Study

The forced degradation study was performed according to the ICH guidelines Q1A (R2).[16] A stock HSS solution (5 mg/mL) was initially prepared and diluted 5-fold, to obtain samples containing 0.1 M HCl, 0.1 M NaOH, 3% H_2O_2, or Milli-Q water. Samples with Milli-Q water were used as controls (ambient temperature and protected from light) and to assess the effect of temperature (60 °C) and light (exposure to daylight). All samples, except those for thermal degradation, were stored at ambient temperature (24 °C) and protected from light (except those for the photostability testing). The samples were exposed to stress conditions for 24 hours. The samples were neutralized with HCl or NaOH (when required) or cooled to ambient temperature (thermal stress samples) before analysis.

2. 4. Preparation of Calibration Standards and QC Solutions

A stock solution containing 5 mg/mL HSS was initially prepared and further diluted with Milli-Q water to obtain calibration standards with the following HSS concentrations: 0.05 mg/mL, 0.5 mg/mL, 2.0 mg/mL, 3.0 mg/mL and 5.0 mg/mL. QC samples containing 0.1 mg/mL, 1.0 mg/mL, and 4.0 mg/mL HSS were prepared from the initially prepared HSS stock solution in triplicate in the same manner. The calibration and QC solutions were prepared and analysed on three consecutive days of the validation.

2. 4. Method Validation

The utilized HPLC–UV method was validated following the ICH guidelines Q2(R1) in terms of specificity, linearity, precision, accuracy, quantitation limit (LOQ), detection limit (LOD), and sample stability.[17]

Specificity was evaluated in chromatograms of the used solvents (Milli-Q water, 0.9% sodium chloride solution, 5% glucose solution, and the solvent in the vial of the medicinal product Solu-Cortef, which contains benzyl alcohol as a preservative), which were compared with the chromatogram of HSS solution. Specificity was also assessed in forced degradation HSS samples, which were evaluated for chromatographic interferences.

Linearity was assessed by linear regression analysis of calibration standards, covering expected HSS concentrations in solutions for infusion (0.05–5.0 mg/mL). The determination coefficient (R^2) > 0.999 was considered acceptable.

The QC solutions, prepared at three concentration levels on each day of the validation, were used to evaluate the accuracy, precision, and injection repeatability. Intra- and inter-day accuracy was determined as the ratio between the HSS concentration calculated from the regres-

sion line and its actual concentration. Intra- and inter-day precision was determined by calculating the relative standard deviation (RSD) of the QC solutions in triplicate and injection repeatability was determined as the RSD of six consecutive injections of a QC solution. The acceptance criteria were 100 ± 5% for accuracy, ≤ 5% RSD for precision, and ≤ 2% RSD for injection repeatability.

The LOD and LOQ were calculated using the equations LOD = (3.3 × σ)/S and LOQ = (10 × σ)/S, where σ is the standard deviation of the intercepts and S is the average slope of the three regression lines.

HSS stability was determined by storing the QC solutions at all three concentration levels in the autosampler (6 °C) and analysing them within 24 h. HSS stability, expressed as a share of the initial response, was set at 100 ± 5%.

2. 6. Sample Preparation and HSS in-use Stability Study in Solutions for Infusion

The stability of HSS was studied in solutions for infusion prepared according to the manufacturer's instructions, and as prepared in our hospital. A 50 mg/mL HSS solution was initially prepared by adding 2 mL of sterile water for injection to the content of a vial of Solu-Cortef, followed by manual shaking. Half of this solution (1 mL) was withdrawn and diluted up to 50 mL with S or G in the original IV containers to an HSS concentration of 1 mg/mL. The 4 mg/mL HSS solutions in S or G were prepared in the same way, using two vials of Solu-Cortef (2 × 2 mL diluted with 50 mL of S or G). The pH values of the prepared solutions were measured using a pH meter MP 220 (Mettler Toledo, Switzerland).

The effects of different HSS concentrations (1 mg/mL and 4 mg/mL), solvent (S and G), temperature (controlled ambient (24 ± 1 °C) and elevated (30 ± 1 °C), and light exposure (protected (UV-prot) and unprotected (UV)) on HSS stability in solutions for infusion were studied (Table 1). All samples were prepared and stored in the original S and G IV containers in triplicate and analyzed at regular time points within 72 hours. All samples were also visually examined for potential physical changes.

Table 1. Conditions during hydrocortisone sodium succinate (HSS) stability study in isotonic saline (S) and 5% glucose (G) solutions for infusion.

Sample	HSS concentration [mg/mL]	Solvent	Storage temperature [°C]	Light exposure
	1	S	24	UV-prot
	4	S	24	UV-prot
	1	G	24	UV-prot
	4	G	24	UV-prot
	1	S	24	UV
	4	S	24	UV
	1	G	24	UV
	4	G	24	UV
	1	S	30	UV-prot
	4	S	30	UV-prot
	1	G	30	UV-prot
	4	G	30	UV-prot

S – isotonic saline (0.9% sodium chloride); G – 5% glucose solution; UV – exposed to daylight; UV-prot – light protected.

2. 7. In-use Stability Determination and Statistical Analysis

The results are expressed as the mean of three parallels of the samples along with the standard error of the mean. Zero ($c = c_0 - kt$), first ($\ln c = \ln c_0 - kt$), and second-order ($1/c = 1/c_0 + kt$) kinetics, where t is time, c is the HSS concentration at time t, c_0 is the initial HSS concentration, and k is the reaction rate constant, were fitted to the HSS degradation using the least square regression function. Among them, the model with the highest R-square was selected and applied for in-use stability determination, which was defined as HSS content ≥ 95% of the initial content. The determined rate constants and in-use stability were compared by 95% confidence intervals. Statistical analyses using a two-sample t-test assuming variances, as previously determined by the F-test for two sets of data, which differ in only one parameter (e.g., different storage temperature, light, HSS concentration, or type of solvent) were performed using MS Excel 2019. Differences with p values < 0.05 were considered significant.

3. Results

3. 1. HSS Forced Degradation Study

Among the conditions tested within the forced degradation study, HSS proved most susceptible to hydrolytic degradation with only 2% remaining in 0.1 M NaOH and 20% in 0.1 M HCl after 24 hours. HSS was also susceptible to oxidation (56% remaining after 24 hours in 3% H_2O_2), thermal degradation (63% remaining after 24 hours of storage at 60 °C), and photolytic degradation to a lesser extent (96% remaining after 24 hours). The HSS main degradation products (t_r 4.0, 5.7, and 6.5 min) formed during the forced degradation study did not interfere with its chromatographic evaluation (t_r 10.9 min) (Figures S1, S2, and S3).

3. 2. Method Validation

The specificity of the method was confirmed as all solvents recommended by the manufacturer for dissolution and dilution of the medicinal product Solu-Cortef, did not contain interfering peaks at HSS retention time. Also, no interfering degradation product peaks were formed during the HSS forced degradation study (Figure S2). In addition, the linearity, intra- and inter-day accuracy and precision,

Table 2. Validation data of the analytical method for hydrocortisone sodium succinate (HSS) quantification.

HSS calibration samples	**Range [mg/mL]** 0.05-5.00	**R^2** 1.0000		**LOD [mg/L]** 12.6			**LOQ [mg/L]** 39.2	
QC samples	**Intra-day accuracy and precision**			**Inter-day accuracy and precision**				
HSS conc. [mg/mL]	**Found conc. [mg/mL]**	**Accuracy (%)**	**RSD (%)**	**Found conc. [mg/mL]**	**Accuracy (%)**	**RSD (%)**	**Inj. rep.**	**Stability (%)**
0.1	0.0981	98.1	1.29	0.0997	99.7	3.30	0.52	100.5
1.0	1.0054	100.5	0.02	1.0087	100.9	0.29	0.20	99.2
4.0	3.9901	99.8	0.46	3.9956	99.9	0.55	0.29	99.2

LOD – detection limit; LOQ – quantitation limit; QC – quality control; conc. – concentration; RSD – relative standard deviation; Inj. rep. – injection repeatability.

and injection repeatability of the method were confirmed (Table 2), as all results were within the acceptance criteria. The method was found sufficiently sensitive for HSS evaluation within the stability study (LOQ ≤ 3.9% of the expected HSS content). HSS also proved proper stability in the QC solutions, with a < 1% change in its response after 24 hours (Table 2).

3. 3. HSS in-use Stability Study in Solutions for Infusion

The determined pH values of the simulated solutions for infusion with different HSS concentrations were as follows: 7.04 in S containing 1 mg/mL HSS; 7.26 in S containing 4 mg/mL HSS; 7.42 in G containing 1 mg/mL HSS and 7.52 in G containing 4 mg/mL HSS and were within the pH range, specified by the manufacturer.[2] The obtained results on HSS stability in the simulated solutions for infusion are shown in Figure 1. The increase in temperature (from 24 °C to 30 °C) significantly increased HSS degradation, while the other tested conditions – different HSS concentrations (1 mg/mL and 4 mg/mL), media (S or G), and light exposure only slightly affected HSS stability. No changes in colour, odour or precipitations were detected in the samples during the stability study.

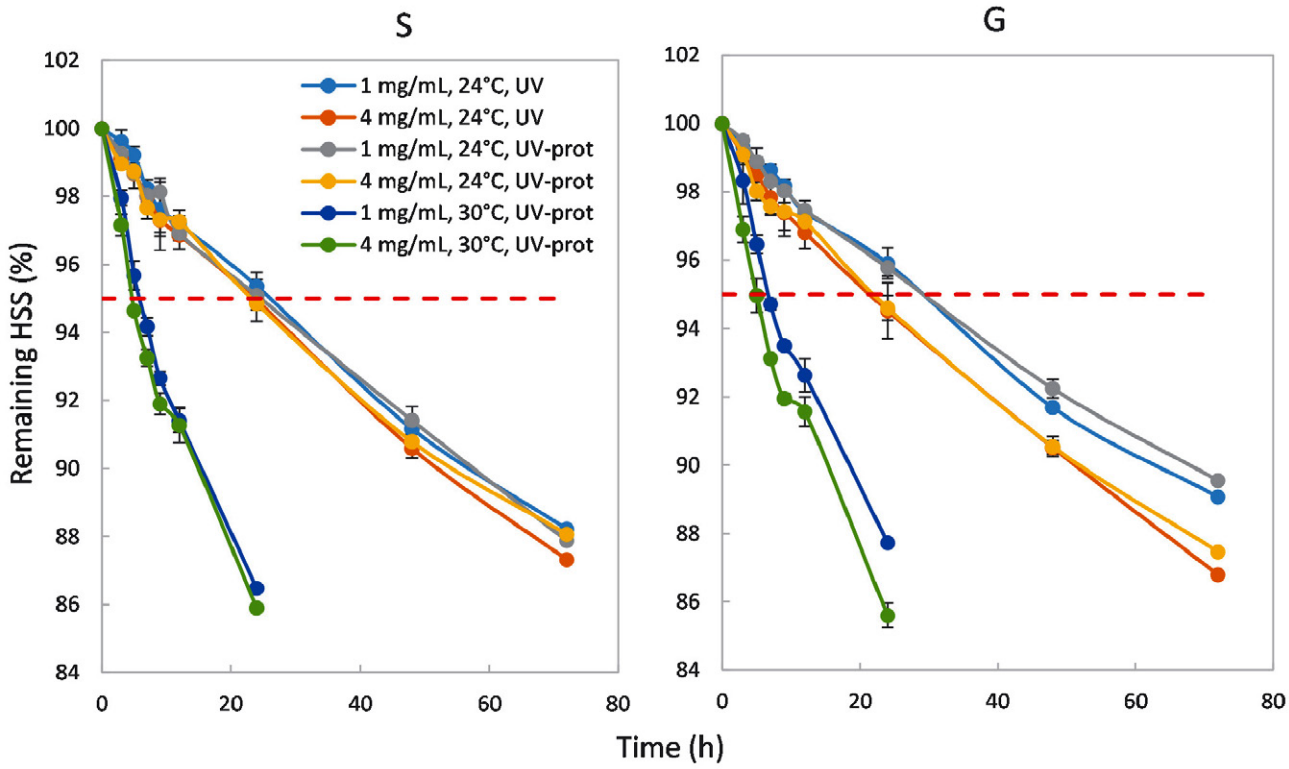

Figure 1. Hydrocortisone sodium succinate (HSS) stability in the simulated solutions for infusion in isotonic saline (0.9% sodium chloride) (S) and 5% glucose solution (G) under different storage conditions. The results are presented as an average ± standard error of the mean, n = 3.

Table 3. First-order rate constants (k_1) and in-use stability ($t_{95\%}$) for hydrocortisone sodium succinate (HSS) at two concentrations (1 mg/mL and 4 mg/mL) in the simulated solutions for infusion under different storage conditions.

Simulated solutions for infusion	k_1 [h^{-1}] (CI) 24 °C, UV-prot	24 °C, UV	30 °C, UV-prot	In-use stability [h] (CI) 24 °C, UV-prot	24 °C, UV	30 °C, UV-prot
1 mg/mL HSS in S	1.84×10^{-3} (1.86×10^{-3} – 2.01×10^{-3})	1.92×10^{-3} (1.90×10^{-3} – 1.93×10^{-3})	8.79×10^{-3} (7.84×10^{-3} – 9.74×10^{-3})	28.0 (**26.6** – 29.3)	26.7 (**26.5** – 27.0)	5.9 (**5.2** – 6.5)
4 mg/mL HSS in S	1.94×10^{-3} (1.86×10^{-3} – 2.01×10^{-3})	1.99×10^{-3} (1.91×10^{-3} – 2.07×10^{-3})	1.03×10^{-2} (9.46×10^{-3} – 1.10×10^{-2})	26.5 (**25.4** – 27.5)	25.8 (**24.7** – 26.8)	5.0 (**4.6** – 5.4)
1 mg/mL HSS in G	1.64×10^{-3} (1.55×10^{-3} – 1.73×10^{-3})	1.76×10^{-3} (1.71×10^{-3} – 1.81×10^{-3})	7.81×10^{-3} (7.46×10^{-3} – 8.17×10^{-3})	31.2 (**29.6** – 32.9)	29.1 (**28.2** – 29.9)	6.6 (**6.3** – 6.9)
4 mg/mL HSS in G	1.98×10^{-3} (1.91×10^{-3} – 2.05×10^{-3})	2.00×10^{-3} (2.00×10^{-3} – 2.05×10^{-3})	1.10×10^{-2} (9.88×10^{-3} – 1.05×10^{-2})	25.9 (**25.0** – 26.9)	25.4 (**25.0** – 25.7)	5.0 (**4.9** – 5.2)

CI – 95% confidence interval; S – isotonic saline (0.9% sodium chloride); G – 5% glucose solution; UV – exposed to daylight; UV-prot – light protected.

The fitting of zero, first, and second-order kinetic models showed that HSS degradation in aqueous solutions follows first-order kinetics, which was applied to its stability evaluation. First-order reaction rate constants were calculated for HSS degradation in each tested solution and used for the determination of its in-use stability (Section In-use stability determination and statistical analysis) (Table 3).

4. Discussion

The main objective of our study was to determine the chemical and physical stability of HSS at two concentrations (1 mg/ml and 4 mg/ml) at ambient temperature after reconstitution with the solvent in the vial of the medicinal product and dilution with 0.9% sodium chloride or 5% glucose solution. Although the HSS concentration of 4 mg/ml exceeds the highest HSS concentration in infusions, prepared according to the manufacturer's instructions, it is a clinically relevant concentration in the treatment of ICU patients, for whom a reduction in the infusion volume is very desirable. These two HSS concentrations represent the most common circumstances, when preparing an HSS infusion, in our hospital and were therefore selected for the study. HSS stability evaluation was performed by utilizing a stability-indicating HPLC-UV method, based on the method proposed in the European pharmacopeia HSS monograph,[18] which was further optimized and properly validated following the ICH Q2(R1) guidelines.[17] The stability-indicating nature of the method was confirmed by forced degradation studies, as the chromatographic peak of HSS was chromatographically separated from its degradation products, as can be seen in Figure S2, yet the peak purity was not assessed due to limitations of the analytical equipment (variable wavelength UV detector). Forced degradation studies also revealed the susceptibility of HSS to degradation under hydrolytic, oxidative, and thermal conditions. However, these stability issues are not addressed by the manufacturer of the medicinal product Solu-Cortef, who does not specify the in-use stability of the HSS solution for infusion. Specified in-use stability would be valuable information for the medical personnel with implications for the patients, as HSS is commonly applied as a continuous infusion. However, it is also unaccounted for in the accessible literature. Therefore, the in-use stability of HSS in solutions for infusion was determined within this study, together with the effects of real-life conditions and situations (use of different types and volumes of solution for dilution, temperature variations, and exposure to light).

The main conclusion from the performed in-use stability study is that HSS stability is mostly affected by temperature, as the increase in temperature (from 24 °C to 30 °C) significantly increased HSS degradation (reaction rate constants in Table 3) and resulted in significantly shorter in-use stability of ≤ 6.3 hours (in-use stability in Table 3) (t-test, $p < 0.001$). The destabilizing effect of higher storage temperature on HSS in S was also demonstrated by Gupta and Ling.[16] The determined in-use stability, considering the 95% confidence interval was higher in the samples protected from light (Table 3). However, these differences were typically not statistically significant (t-test, $p > 0.05$), which is in line with the findings from the performed forced degradation study (Section HSS forced degradation study). Analogously, the differences between the stability of HSS at different concentrations in S were not significant (t-test, $p > 0.05$), whereas G containing a higher HSS concentration (4 mg/mL) was significantly less stable than the 1 mg/mL solution (t-test, $p < 0.03$) under all three evaluated conditions (24 °C, protected from light; 24 °C, exposed to daylight; and 30 °C, protected from light) (Table 3). Comparing the HSS stability in solution with the same concentration and stored under the same conditions

(Table 3), we concluded that the use of different dilution solvents (S or G) does not significantly affect the HSS stability (t-test, $p > 0.05$), which was expected as they are both recommended as dilution solvents by the manufacturer.[2] The determined in-use stability of 24 hours under controlled room temperature provides the medical personnel reliable evidence on the usability of the infusion solution, during the application of the infusion. During this time period, all evaluated HSS solutions remained physically stable, as no changes in the organoleptic properties were observed. The microbiological stability was not evaluated within this study. The results of this stability study, performed in clinically relevant conditions on the medicinal product, represent a step forward in providing high-quality patient care, which is primarily ensured by the quality of the medicinal product itself, guaranteed by its manufacturer and the competent regulatory bodies.

5. Conclusion

The chemical and physical stability of HSS in solutions for infusion under different conditions, which simulate the conditions in hospitals, was assessed within this study. The results, obtained using a stability-indicating HPLC-UV method, revealed HSS degradation in these solutions, which followed first-order kinetics. Based on the stability data, in-use stability ($t_{95\%}$) of at least 24 hours was confirmed at ambient temperature and a significantly lower in-use stability (≤ 6 hours) at 30 °C. Other evaluated conditions (HSS concentration, light exposure, and use of different dilution solvents), did not significantly affect the stability of HSS in the examined solutions for infusion. All evaluated solutions were physically stable within the determined in-use stability. The significant temperature effect on the stability of HSS in solutions for infusion should be considered in hospitals with uncontrolled temperatures and especially during summertime.

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Competing interest: None declared.

6. References

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Povzetek

Namen te študije je opredelitev stabilnosti in določitev roka uporabnosti med uporabo ($t_{95\%}$) raztopin za infundiranje z natrijevim hidrokortizonsukcinatom (HSS) ter zagotovitev na dokazih podprtih priporočil o njihovi uporabnosti.

Infuzijske raztopine HSS smo pripravili in shranjevali v skladu s priporočili proizvajalca in pri običajnih pogojih v naši bolnišnici. Z validirano stabilnostno indikativno HPLC-UV metodo smo ugotavljali vpliv koncentracije HSS (1 in 4 mg/mL), topila (izotonična fiziološka raztopina in raztopina glukoze), temperature (sobna in 30 °C) in svetlobe na njegovo stabilnost.

Razgradnja HSS je sledila kinetiki prvega reda. Ugotovili smo, da različni preiskovani koncentraciji HSS, obe topili in izpostavljenost svetlobi niso značilno vplivali na stabilnost HSS ($t_{95\%}$ med 25 in 30 urami), medtem ko je povišana temperatura (30 °C) značilno skrajšala $t_{95\%}$ (4,6–6,3 ur).

Infuzijske raztopine HSS so fizikalno in kemično stabilne (<5 % razgradnja) vsaj 6 ur pri temperaturi do 30 °C in najdlje 24 ur pri temperaturi do 24 °C.