The stability of ready-to-use (RTU) ephedrine hydrochloride in polypropylene syringes for use in maternal hypotension

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ABSTRACT
A ready-to-use intravenous syringe of ephedrine hydrochloride for use in emergency situations in maternal hypotension was prepared under aseptic conditions in the hospital pharmacy. The chemical stability of this solution (20 mg/2 mL) in 0.6% sodium chloride was determined at 25°C and 40°C by means of a stability indicating high-performance liquid chromatography method. The pH was measured throughout the study and presence of particulate matter was controlled. Sterility testing was performed to test the integrity of the syringes. The loss in potency was less than 5% after 12 months at both temperatures and no degradation products were detected. The pH values did not change appreciably and the syringe contents remained sterile throughout the study. Particulate matter was well within pharmacopoeial limits. In conclusion, ready-to-use syringes of ephedrine hydrochloride with a long shelf-life can be manufactured and supplied by the hospital pharmacy for emergency use in obstetrics.

KEY WORDS
Ephedrine, drug stability, polypropylene syringes, CIVAS, obstetrics

INTRODUCTION
Lumbar epidural analgesia or spinal analgesia are now frequently prescribed during labour. Maternal hypotension is perhaps the most common complication of regional analgesia and anaesthesia and should be treated rapidly to avoid foetal distress [1]. Ephedrine is one of the two vasopressors of choice along with phenylephrine, and it must be administered immediately to correct hypotension [2-4]. Until recently in our hospital [5], syringes were prepared extemporaneously by anaesthetists or nursing staff by transferring the contents of 2 mL ampoules into syringes that were placed at the bedside of every parturient. Preparation in obstetrics in such conditions is time-consuming and can increase errors [6] and/or risk of infection [7,8]. It has been found in some cases that syringes have been prepared on the wards the day before, and in other cases have been kept for use the following day [9]. Furthermore these solutions prepared in advance can increase costs due to wastage (unused syringes are discarded at the end of the day). The aim of this investigation was to develop a long shelf-life ready-to-use (RTU) ephedrine syringe prepared under aseptic conditions, supplied by the hospital pharmacy that can be put back into stock for another patient if not used.

MATERIAL AND METHODS
Preparation of the syringes for stability studies
A solution of 0.6% sodium chloride in water for injection containing 20 mg/2 mL of ephedrine hydrochloride Ph. Eur. (Hänseler, Herisau, Switzerland) was prepared. It was filtered (0.22 µm) and 2 mL were transferred into 2.5 mL polypropylene syringes (PlastiPak Becton Dickinson, NJ, USA) under a laminar-airflow hood in a GMP class B cleanroom. The syringes were stoppered using tamper evident caps (TEC 1000 B Braun Melsungen, Germany) and individually packed into plastic sachets. They were stored at 25°C ± 2°C and 40°C ± 2°C. The solutions were assayed immediately after preparation of the syringes (day 0) and after 2, 3, 6 and 12 months.

HPLC analysis
Chromatographic equipment and conditions
The method was developed by the Quality Control laboratory of the Pharmacy, University Hospitals of Geneva, Switzerland by adapting the methods of Imaz et al [10] and Hood and Chung...
[11]. The HPLC system was a Merck-Hitachi LaChrom D7000 HSM (HPLC System Manager) using a L7100 high pressure pump. Separations were carried out on an RP100 C8 (5mm) LiChrospher column: 125 x 4.6 mm (Merck cat no. 50942). The mobile phase consisted of 0.01M potassium dihydrogenphosphate pH 3.0 buffer (Merck 4873), acetonitrile (Merck 1.14291) and diethylamine (Merck 3010) 900:100:1. The final pH was adjusted to pH 5.0 ± 0.1 with HPLC grade 0.1N phosphoric acid. The flow rate was 2.0 mL/min, the eluent was monitored at 215 nm and the temperature was ambient. 20 µL of the assay solutions and the standard solutions were injected into the chromatograph. The assays were performed in triplicate. The results were calculated automatically by the LaChrom D7000 HSM using peak area determination.

**Validation of the HPLC method**

The chromatographic method was validated according to SFSTP guidelines [12] before applying it to the stability study of the RTU ephedrine hydrochloride solution. Standard (std) and reconstituted formulation (rf) solutions at five ephedrine hydrochloride concentration levels (50, 75, 100, 125, and 150 µg/mL) were prepared daily and used to test linearity and accuracy. Six different rf solutions at 100 µg/mL corresponding to 100% of ephedrine hydrochloride present in the formulation were prepared each day and used to determine the precision of the method. Validation results are summarized in Table I. Slopes and intercepts were not significantly different for rf and std samples (t tests). Moreover, intercepts were not significantly different from 0 (t test). All the statistical tests were positive thus verifying the linearity and accuracy of the method. Good determination coefficients (r²), recoveries and precision values were also obtained (Table I). Thus, the method was accepted for determining ephedrine hydrochloride concentrations in RTU intravenous plastic syringes.

<table>
<thead>
<tr>
<th>Table I: Validation results of the ephedrine hydrochloride assay</th>
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<tr>
<td>Ephedrine hydrochloride</td>
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<tr>
<td>Determination coefficients for std and rf: 0.9989 / 0.9992</td>
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<tr>
<td>Mean recovery and confidence interval*: 99.41% ± 0.81%</td>
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<tr>
<td>Intra-day precision: 0.90%</td>
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<td>Day-to-day precision: 1.08%</td>
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<td>*(N = 15, t (0.05; N-1) = 2.145)</td>
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**Stability indicating method**

To rule out possible interference of degradation products during the ephedrine hydrochloride determination, 1 mL of both a 1N sodium hydroxide solution and a 1N hydrochloric acid were added to 1 mL of the ephedrine hydrochloride mother solution respectively. The solutions were heated at 100°C in a water bath for two hours and 200 µL were diluted in 10 mL of the mobile phase. In order to check the absence of decomposition products eluting under the analyte peak, the peak height/area ratio was compared at two different detection wavelengths (214 and 257 nm) with a pure ephedrine hydrochloride standard.

**Sample preparation during the stability study**

Stock solutions containing 5 mg/mL of ephedrine hydrochloride Ph. Eur. (Hänseler, Herisau, Switzerland) and 10 mg/mL of procaine hydrochloride Ph. Eur. (Hänseler, Herisau, Switzerland) (internal standard) were prepared in distilled water. Standard samples were prepared by diluting the stock solutions in the mobile phase to obtain an ephedrine concentration range of 50–150 µg/mL and a procaine concentration of 200 µg/mL. The ephedrine hydrochloride assay solution (syringe) at 20 µg/mL was diluted in the mobile phase to obtain a final concentration of 100 µg/mL. As in the case of the calibration samples, procaine hydrochloride was added to the assay solution as internal standard at 200 µg/mL.

**Sterility testing**

The tests were performed using a method developed by the Quality Control laboratory, Pharmacy, University Hospitals of Geneva, Switzerland [13]. Ten syringes at both temperatures were tested for sterility at the beginning and the end of the study.

**pH determination**

The pH of the solutions was measured at each time interval with a glass electrode pH meter (Metrohm model 691, Herisau, Switzerland).

**Particulate matter**

A HIAC Royco counter with a HRLD-50 sensor module (serial no. 95080045) was used for the particle count determinations. Four runs were carried out and the results of the 1st run were discarded. The particle counts were performed at day 0 on 10 mL samples obtained by pooling several syringes.

**Results**

Only the ephedrine hydrochloride peak was seen on the chromatograms of the acid and base degraded samples. The ratio values of the analyte peak after basic decomposition to a fresh ephedrine hydrochloride standard were 1.00 and 0.99 at 214 and 257 nm, respectively. For acid decomposition, ratio values were 0.99 and 1.01 at 214 and 257 nm, respectively. These results confirmed the purity of the analyte peak. Figure 1 represents a typical chromatogram of RTU ephedrine hydrochloride solution in 0.6% NaCl after 12 months at 25°C. The injections were considered to be stable if the drug levels remained higher than 90% of the original concentration at the time of preparation. The results were found to be above 95% after 12 months at both 25°C and 40°C (Figure 2). The pH decreased slightly throughout the study at both temperatures to an average 0.39 pH units at 25°C and 0.43 pH units at 40°C (initially pH 6.0). These changes
had no effect on the assay results. The sterility tests were found to be negative in all cases and particle counts were well within the limits specified by the European Pharmacopoeia. The admixture remained clear throughout the whole study period.

**DISCUSSION**

It is well known that ephedrine hydrochloride is extremely stable in aqueous solution as it can be autoclaved in glass containers (ampoules and vials) at 120°C with a resulting shelf life of several
years. The objective in developing an RTU syringe was to ensure the best possible quality for the patient. This contrasts with the previous situation where syringes were prepared in advance in the wards or operating theatres with risk of error and/or contamination. To the best of our knowledge, all published stability studies concerning ephedrine hydrochloride in syringes were carried out for periods not longer than two months [14] which is logistically relatively short (stock control for example) in comparison with other drugs. The situation could lead to expired syringes in both ward stocks and at the bedside as well as numerous batches being prepared leading to greater chances of contamination. Due to the limitations of our hospital pharmacy production unit, larger-scale batch production is envisaged in the future through outsourcing. For the aforementioned reasons we carried out a long-term study that proved that the ephedrine hydrochloride solution was stable after 12 months even under accelerated degradation conditions (40°C). This approach raises the question of bacterial contamination, during aseptic production and/or after storage due to loss of syringe integrity. Bacterial contamination is a risk inherent to aseptic production and must be avoided by strict application of GMP requirements. These include in particular: regular environmental controls, initial and continuing education of operators and also process validation through media-fill simulations as shown in a recently published study [15]. Syringe integrity was demonstrated by the negative results obtained from sterility tests carried out during the stability testing period. Our experience has shown that no incidents have been declared after the use of nearly 20,000 RTU syringes in our hospital.

**Conclusion**

Ready-to-use syringes supplied by the hospital pharmacy and stored in obstetrics were found to be stable at room temperature for at least 12 months with no significant loss in potency. Unused syringes in the original unopened sachets can be returned to stock and made available for other patients. This long shelf-life is very helpful to optimise production batches and it should also contribute to save time for hospital staff and reduce costs due to wastage. Furthermore, the availability of pre-filled syringes decreases the delay required to draw up the drug in emergency situations and can reduce the risks of errors and/or infection.

**References**