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Pharmacy based preparation and stability of ready-to-administer epinephrine injection solution (0.02 mg/mL, 50 mL)

Background and Purpose

In the University Medical Center Mainz standardized concentrations are determined for all medicinal products that are administered by continuous injection in adult intensive care patients. Patient individual doses are provided by adjusting the injection rate. A number of the ready-to-administer products are aseptically prepared in the hospital pharmacy department. The aim of this project was to test the feasibility of batch-wise semi-automated aseptic preparation of epinephrine injection solutions 0.02 mg/mL in 50 mL plastic syringes and to validate the analytical methods for quality control and stability testing of the finished product.

Materials and Methods

Bulk solution containing epinephrine hydrochloride 20 µg/mL (batch size 80 syringes = 4 L) was prepared in a closed procedure by dilution of licensed epinephrine 25 mg/25 mL (concentration 1 mg/mL) injection concentrate. The calculated amounts of the injection concentrate and 5% glucose infusion solution are mixed in empty infusion bags (PP/PE). The bulk solution is aseptically filled with a four-channel-syringe pump into lightproof 50 mL syringes as primary containers and closed with stoppers (s. Fig. 1). The syringes are semi-automatically labelled (s. Fig. 2) and stored at 2-8 °C.

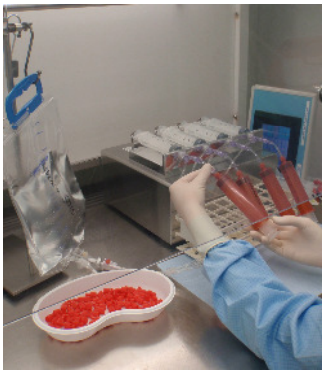
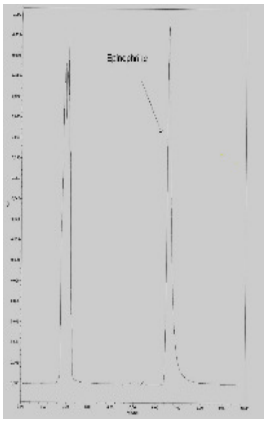


Fig.1: Filling with a four-channel-syringe pump

Fig.2: Semi-automated labelling

Samples of each batch are withdrawn for sterility tests and measurement of the epinephrine concentration. Therefore a HPLC assay with UV detection at 280 nm and an innovative Nucleodur sulfonyl group HPLC column was implemented and validated. Stability tests were performed with the same assay.



HPLC Assay

Column: Nucleodur HILIC® 5 µm, 250 x 4.6 mm

Mobile phase: 25% ammonium acetate buffer
75% Acetonitril

Injection volume: 100 µl

Flow rate: 1.5 ml/min

UV/Vis-Detection : 280 nm

Linearity: 0.9997

Accuracy: 100% ± 1,87

Intraday Precision [RSDr]: 1.87%

Interday Precision [RSDt]: 2.88%

Fig. 3: HPLC Chromatogram of Epinephrine 20 µg/ml, UV/VIS- Detection at 280 nm

Results

Stability tests of the ready-to-administer epinephrine injection solution 0.02 mg/mL, 50 mL were performed over a six month period. After 28 days, 3 months and 6 months of storage under refrigerated conditions the concentration amounted to 100.6%, 100.7%, and 97.6% of the initial concentration, respectively. After 7 months of storage the concentration of epinephrine declined to 92.2% of the initial concentration (s. Fig.5)

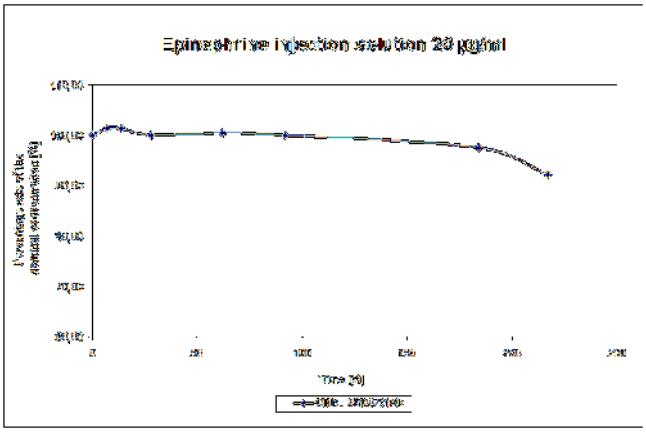


Fig. 4: Stability of epinephrine injection solution 20 µg/mL over 6 months under refrigeration

Neither adrenochrome (detection wavelength 480 nm)[1] nor any other degradation product was detected during the study period.

The semi-automated procedure revealed to be adequate in order to prepare the ready-to-use syringes complying with the specifications set. The preparation of one batch i.e. 80 syringes (compare Fig. 5) takes one hour. With reference to the proven physicochemical stability, stock preparation of ready-to-use ephinephrine injection solutions is feasible in the hospital pharmacy department, time-saving in the intensive care units and ensures patient safety.

Fig.5: Batch-wise produced epinephrine syringes (0.02 mg/mL, 50 mL)

Conclusions

The batch-wise aseptic preparation of epinephrine injection solution 0.02 mg/mL, 50 mL as well as adequate quality control measures and batch release are feasible in an efficient manner in the hospital pharmacy department. Physicochemical stability is given over at least six months under refrigerated storage conditions. The accurate, safe and stockable ready-to-administer products are highly appreciated by doctors and nurses.

Literature

[1] Bindoli, A. Deeble, D.J. Et al; Direct and respiratory chain-mediated redox cycling of adrenochrome; Biochimica et Biophysica Acta 1990; 1016: 349-356