IMPLEMENTATION AND QUALITY CONTROL OF A 5% FRUCTOSE AND 10% GLYCEROL STERILE SOLUTION FOR DIGESTIVE ENDOSCOPY

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Background Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are innovative digestive endoscopic approaches allowing ‘en bloc’ tumour removal – which facilitates histological analysis and lowers the risks of local relapse. To ease complete tumour removal, both techniques require submucosal fluid injections. Nevertheless, no ready-to-use commercial solutions for submucosal injection are available.

Purpose To implement a simple production of a ready-to-use 5% fructose and 10% glycerol sterile solution (FGSS) for submucosal injection and appropriate quality controls.

Material and methods FGSS were aseptically compounded according to good manufacturing practices. Fructose and glycerol were mixed with isotonic sodium chloride in an ISO 5 controlled atmosphere area. The solution was sterile-filtered using rapid flow 0.22 m filter units (ThermoScientific) and aseptically-filled into glass containers (125 mL) in a vertical laminar flow hood. An alternative method, using terminal sterilisation (121°C for 20 min), was also tested.

Quality controls were performed on three vials (beginning-middle-end of production). Fructose and glycerol concentrations were assessed by colorimetric-enzymatic methods adapted on a chemistry analyser (acceptance limits±10%). We developed a method of quantifying two fructose degradation products (5-hydroxymethylfurfural (5HMF) and 2-furaldehyde (2FA)) in FGSS, using a high-performance liquid chromatography UV Diode-Array-Detector. Accuracy profile serves for validation (relative acceptance limits±10%). Sterility assay and endotoxin testing (kinetic chromogenic method) were performed. Sub-visible particles contamination was assessed using a light-obscuration method (European pharmacopoeia (EP) 2.9.19 threshold: respectively 25 and 3 particles/mL for particles size ≥10 μm and ≥25 μm).

Results Our sterile-filtered compounding method allows the production of a sterile and bacterial-endotoxin-free FGSS. Particle load was 9.99 and 0.37 particles/mL respectively for ≥10 μm and ≥25 μm particles. Fructose and glycerol concentrations (g/L) were respectively at (mean (min-max)) 48.99 (47.04–50.39) and 127.39 (123.4–129.8). Both 5HMF and 2FA concentrations were below our method’s limits of quantification (3.39 and 1.69 mg/mL respectively). When using the moist heat sterilisation method, the solution became light yellow and 5-HMF was 19.61 mg/L (far above EP specification).

Conclusion Our compounding method is simple, limits 5HMF production and can be implemented in any hospital. Produced FGSS complies with the EP quality requirements. We developed the first specific and sensitive method for 5HMF and 2FA concentrations measurement in a FGSS preparation.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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PHYSICOCHEMICAL STABILITY OF NOREPINEPHRINE BITARTRATE IN POLYPROPYLENE SYRINGES AT HIGH CONCENTRATIONS FOR INTENSIVE CARE UNITS

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Background Norepinephrine is usually used in emergency situations as in intensive care units (ICUs) for the restoration of blood pressure. High doses at 3–5 μg/kg/min can be used in the treatment of septic or hemorrhagic shock.

Purpose The objective was to study the stability of high concentrated solutions of norepinephrine at 0.50 mg/mL and 1.16 mg/mL, diluted in glucose 5% (G5%) in polypropylene syringes, protected or not from light, after the preparation and after a 6 hour, 24 hour and 48 hour storage at room temperature.

Material and methods Chemical stability was analysed by high-performance liquid chromatography coupled to a photodiode array detector at each time of analysis. The method was validated according to the International Conference on Harmonisation Q2 (R1). Physical stability was evaluated by visual and subvisual inspection (turbidity by UV spectrophotometry at 350, 410 and 550 nm as recommended by the European Consensus Conference). Three syringes for each condition were prepared. At each time of analysis, three samples were prepared and analysed for each syringe. pH values were evaluated at each moment of the analysis.

Results Solutions of norepinephrine at 0.50 and 1.16 mg/mL, diluted in G5%, with or without protection from light, retained more than 95% of the initial concentration after 48 hours of storage at 20°C–25°C. Solutions remained clear, without change of colour or precipitation during the study. Concerning turbidity assays, values of absorbance remained inferior to 0.010 AU. No degradation product appeared during stressed degradation was observed during the study, but an additional peak with a retention time at 3.8 min was observed and constant. This peak was equally observed on chromatograms of the G5% solution. A solution of 5-hydroxymethylfurfural (5-HMF), a degradation product of glucose, was prepared and analysed by HPLC. The retention time was also

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