

Material and methods The pharmaceutical specialty composed of insulin aspart and its two preservatives (phenol and metacresol) were diluted in saline or D5%. The impact of the diluent on the stability of insulin aspart was studied by high-performance liquid chromatography with UV detection (HPLC-UV). A stability indicator method,¹ adapted from the method of Poulsen *et al.*² and developed for insulin aspart diluted in saline, was used. The prospective formation of a new compound in the different diluents was evaluated by HPLC with a mass spectrometry detection (HPLC-MS) in full-scan mode. The kinetic of the new compound's appearance was studied by relative evaluation of HPLC-UV signals during 1 week for insulin at 1 U/mL diluted in D5% (n=4).

Results The three products contained in the pharmaceutical specialty diluted in saline correspond to the three signals identified in HPLC-UV (elution order: phenol, metacresol and insulin aspart). After dilution of insulin aspart in D5%, we noted a fourth signal. pH influence and forced degradation tests failed to attribute this signal to insulin or preservatives' degradation. HPLC-MS analysis revealed a mass difference of 162 daltons between insulin and this product, which corresponds to a glycation phenomenon of insulin aspart. Finally, the kinetics shows that the insulin glycation phenomenon seems to increase with the contact time between insulin and glucose until a plateau is reached after 24 hour of contact.

Conclusion This work highlighted the instability of insulin in D5% and showed the phenomenon of insulin aspart glycation. To better characterise this phenomenon, the biological effect of glycation on insulin activity have to be determined, since a decrease in activity has been observed for human insulin.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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No conflict of interest.

3PC-005 STABILITY STUDY OF A 10% SODIUM BENZOATE ORAL SOLUTION

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Background Defects in the urea cycle are genetic diseases in which nitrogen accumulates as ammonia, resulting as highly toxic, especially in paediatric patients. Sodium benzoate (SB) is conjugated with glycine, giving rise to hippurate, which is excreted in the urine. Currently there are only intravenous SB commercial presentations, but no oral preparation is commercialised. Due to this, its manufacture in hospital pharmacy services is necessary.

Purpose The main objective is to evaluate the stability of an oral solution of 10% SB at different storage conditions for the treatment of urea cycle disorders in paediatric patients.

Material and methods Initially, six 10% SB samples were prepared from the commercial SB powder (Acofarma) and sterile water. Three were kept at room temperature and three were stored at 2°C–8°C during 30 days, protected from light. On the other hand, SB was characterised spectrophotometrically in water, to obtain a calibration curve. We studied

several physical and chemical parameters after preparation (day 0) and after 7 and 30 days. These parameters were colour, opacity and the presence of precipitation, absorbance and pH. Each preparation was visually inspected in front of a black and white background. pH measurements were carried out by pH indicator strips. All absorbance measurements were obtained after dilution of solutions, with a Shimadzu spectrophotometer model UVmini-1240 UV-Vis.

Results All 10% SB solutions were initially homogenous and transparent. A calibration curve was obtained at 223 nm ($y=56\,495x+0.0177$; $R^2=0.9995$), with an average recovery percentage of 99.92% (SD=1.21; CV=1.21). On day 7 post-elaboration, an average degradation of 1.49% of active ingredient was observed in room-temperature stored samples and 2.82% in refrigerated samples. On day 30, the percentage of loss increased to 2.55% and 3.48% respectively. After 30 days, no colour change, no opacity and no precipitation were observed. In all test solutions the pH-values remained unchanged.

Conclusion The results allow us to conclude that our 10% SB oral solution, used in urea cycle defects in paediatric patients, are physically and chemically stable for at least 30 days when stored at room temperature or at 5°C±3°C with protection from light.

REFERENCES AND/OR ACKNOWLEDGEMENTS

N/A.

No conflict of interest.

3PC-006 ANALYSIS OF THE REGIMENS ESTABLISHED AT THE PHARMACY SERVICE FOR TOTAL PARENTERAL NUTRITION AND THE USE OF GLUTAMINE AS A SOURCE OF NITROGEN

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Background The recommendations for the appropriate composition of total parenteral nutrition (TPN) for adult patients with different pathologies have been changing over the years as new studies are conducted, tending to be higher in protein and lower in total kilocalories.

Different guidelines such as the European and the American Society of Parenteral and Enteral Nutrition (ESPEN and ASPEN) or the Canadian Clinical Practice Guidelines are referents on the subject.

Purpose To analyse the accuracy of the regimens established at the pharmacy service for TPN in 2011 regarding the amount of protein, and also to evaluate whether glutamine is being used as supplementation or as a source of nitrogen to meet the recommendations.

Material and methods A retrospective study covering the period from January 2018 to August 2018 was conducted in a University Hospital evaluating the prescriptions of TPN and whether they were supplemented with glutamine or not. Data were collected from an Acces base designed for the elaboration of the TPN bags.

Then, a review of the total amount of nitrogen in the regimens was conducted.

Results A total of 2296 prescriptions of TPN were received at the pharmacy service. Regarding these prescriptions, 1121

(48.8%) were elaborated for non-critical patients and 1085 (51.2%) for the Critical Care Unit.

Concerning glutamine addition, 970 (86.7%) of the bags for non-critical patients were supplemented with glutamine and 446 (41.1%) bags for the Critical Care Unit were supplemented as well.

Without supplementation, the maximum amount of nitrogen available in the dosage regimes is 14 g and, with supplementation, it can rise to 18 g.

Conclusion Since the recommendations of total protein are higher (1.2–2 g nitrogen/kg/day ASPEN2016) than some years' ago (1.3–1.5 g nitrogen/kg/day ESPEN2009) it seems clear that the available regimens of TPN at the pharmacy service are outdated, and glutamine is being used not only as supplementation but also as a source of nitrogen.

In the light of the results, new products high in nitrogen (16 g and 18 g) and new regimens were proposed to limit the use of glutamine only as supplementation and improve the adherence to the Guidelines.

REFERENCES AND/OR ACKNOWLEDGEMENTS

No conflict of interest.

3PC-007 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 µm 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 ng/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

No conflict of interest.

3PC-008 PHYSICO-CHEMICAL 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 (turbidimetry 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