Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis 39 (2005) 339–343
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Shelf lives of aseptically prepared medicines—Stability of piperacillin/tazobactam in PVC and non-PVC bags

Diane Clare Rigge *, Martin Frederick Jones

Quality Control North West, Stepping Hill Hospital, Poplar Grove, Stockport, Cheshire SK2 7JE, UK

Received 23 January 2005; received in revised form 19 March 2005; accepted 19 March 2005
Available online 26 April 2005

Abstract

Parenteral aseptic preparations of piperacillin/tazobactam are used frequently in hospitals, but there is limited published information on their stability in polyvinyl chloride (PVC) and polyolefine laminate (non-PVC). The purpose of this study was to evaluate the stability in these containers and to determine the optimum validated shelf life so that the formulations may be prepared in bulk in appropriately licensed facilities.

In the first study, the stability of piperacillin/tazobactam 45 mg/ml was determined in polyvinyl chloride and polyolefine laminate bags in 0.9% (w/v) sodium chloride at 7 °C, 25 °C/60% relative humidity (RH) and room temperature in the light (RTL) with storage up to 41 days for PVC bags and 98 days for non-PVC bags. In the second study, the stability of piperacillin/tazobactam 45 mg/ml was determined in non-PVC bags in a buffered sodium chloride formulation at 7 °C, 25 °C/60% RH and RTL with storage up to 201 days.

Samples from each admixture were analysed for piperacillin concentration, tazobactam concentration and appearance of decomposition products by stability indicating high-performance liquid chromatography (HPLC). The pH and appearance of solution and container were also monitored.

Shelf lives were calculated using the maximum rate method. Tazocin™ was found to be stable in 0.9% (w/v) sodium chloride in PVC bags for up to 5 days at 7 °C and 4 days at both 25 °C and RTL. In non-PVC bags, it was stable for 17, 4 and 3 days, respectively. It was stable in the buffered sodium chloride formulation in non-PVC bags for up to 58 days at 7 °C, 10 days at 25 °C and 7 days at RTL.

Keywords: Piperacillin; Tazobactam; Tazocin; Stability; Shelf life

1. Introduction

Piperacillin (Fig. 1) is broad-spectrum semi-synthetic penicillin active against Gram positive and Gram negative bacteria. It is susceptible to hydrolysis by a range of β-lactamases. These enzymes inactivate β-lactam antibiotics by opening the β-lactam ring. Piperacillin is usually administered with tazobactam (Fig. 2), a penicillanic acid sulphone derivative that is a potent β-lactamase inhibitor.

Piperacillin/tazobactam combinations are used in the treatment of infections of the urinary tract, intra-abdominal infection, skin infections and bacterial septicaemia. It is given intra-venously in a ratio of piperacillin (as sodium salt) 8:1 tazobactam (as sodium salt), and is manufactured as Tazocin™ (4 g piperacillin, 0.5 g tazobactam).

Tazocin™ is frequently administered by intra-venous injection or infusion, usually after dilution in 0.9% (w/v) sodium chloride. In order to avoid the dose mismanagement and microbiological hazard of preparation in clinical areas, these solutions can be prepared in validated licensed aseptic facilities under the control of a pharmacist. For this to be viable, batch production needs to be adopted, which in turn relies on a long shelf life being available.

Mathew et al. [1] showed that piperacillin 60 mg/ml with tazobactam 7.5 mg/ml in 50 ml PVC bags, in both 0.9% (w/v) sodium chloride and 5% dextrose was stable for 2 days at 25 °C and 28 days at 5 °C.

* Corresponding author. Tel.: +44 161 4195011; fax: +44 161 4195394.
E-mail address: Diane.Rigge@stockport-tr.nwest.nhs.uk (D.C. Rigge).

0731-7085/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2005.03.013

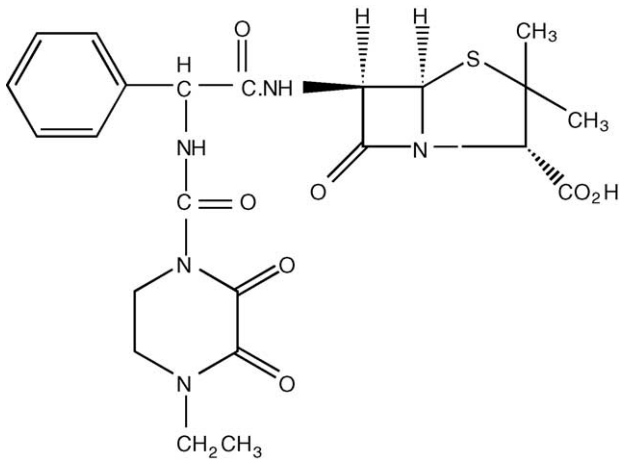

Fig. 1. Structure of piperacillin.

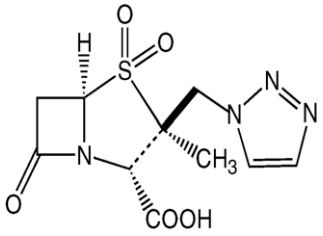

Fig. 2. Structure of tazobactam.

Das Gupta et al. [2] showed that piperacillin sodium 10 mg/ml in both 0.9% (w/v) sodium chloride and 5% dextrose in PVC bags was stable for 2 days at 25 °C, 28 days at 5 °C and at least 71 days at −10 °C.

Moon et al. [3] showed that piperacillin 150 mg/ml and 200 mg/ml with tazobactam 18.75 mg/ml and 25 mg/ml in polypropylene syringes in both 0.9% (w/v) sodium chloride and 5% dextrose were stable for 1 day at 25 °C, 7 days at 4 °C and 30 days at −15 °C. They also showed that piperacillin 80 mg/ml with tazobactam 10 mg/ml in PVC minibags was stable in both diluents for 30 days at −15 °C.

There was a need for a more prolonged and detailed study to allocate a maximum shelf life appropriate for the infusion formulations.

2. Experimental

2.1. Materials and reagents

All commercial reagents and materials were obtained from VWR International Ltd. (Lutterworth, England). Piperacillin analytical standard was purchased from Sigma–Aldrich Company Ltd. (Poole, England). Tazocin™ 4.5 g vials were kindly donated by Wyeth Pharmaceuticals (Maidenhead, England). Polyvinyl chloride (PVC) 100 ml bags and polyolefine laminate (non-PVC) 100 ml bags containing 0.9% (w/v) sodium chloride were kindly supplied by Baxter Healthcare Ltd. (Thetford, England). Non-PVC 100 ml bags were purchased from Sengewald GmbH (Halle, Germany) and filled with an isotonic mixture of a citrate buffer and 0.72% sodium chloride with a nominal pH of 7.0 (buffered sodium chloride) by Preston Pharmaceuticals (Preston, England).

2.2. Apparatus and chromatographic conditions

The high-performance liquid chromatographic (HPLC) system (Thermo Electron, Hemel Hempstead, England) consisted of a vacuum degasser, binary gradient pump (P200), autosampler fitted with sample preparation (AS3000) and a UV–vis detector (UV150). Chromatographic results were collected by data handling software (Scientific Software Inc., EzChrom Elite Version 2.61, Aston Scientific Ltd., Stoke Mandeville, England). Measurements of pH were carried out using a combination electrode pH meter (Corning, Model 120, Halstead, England). The chromatographic separation was performed at ambient temperature on a reversed phase Platinum EPS C18 column (Alltech Associates Inc., Carnforth, England) 250 mm × 4.66 mm i.d., 5 μm particle size. Elution was established with a mobile phase composition of acetonitrile and water (35:65, v/v) containing 0.4% tetrabutylammonium hydroxide pH 3.5 at a flow rate of 1.0 ml/min. The chromatographic signal was monitored at 230 nm. The injection volume was 10 μl.

2.3. Standard and sample solutions for HPLC analysis

For the assay of piperacillin, piperacillin sodium in water at a nominal concentration of 1 mg/ml (as piperacillin free acid) was further diluted in water to give a final injection concentration of 0.1 mg/ml. For the assay of tazobactam, a specified and reserved batch of Tazocin™ powder for injection was used. Tazocin™ in water at a concentration equivalent to 0.13 mg/ml tazobactam free acid was further diluted in water to give a final injection concentration of 0.013 mg/ml tazobactam.

Samples were diluted in water to give a final injection concentration of 0.08 mg/ml piperacillin and 0.01 mg/ml tazobactam.

All dilutions were carried out using the autodilution and sample preparation function of the autosampler.

2.4. Preparation of admixtures

Tazocin™ 4.5 g was reconstituted with 20 ml of 0.9% (w/v) sodium chloride or buffered sodium chloride taken from a 100 ml i.v. infusion bag. After reconstitution, the solution was replaced in the appropriate bag giving final concentrations of 40 mg/ml piperacillin and 5 mg/ml tazobactam.

2.5. Stability study protocol

Two PVC and two non-PVC bags each containing Tazocin™ in 0.9% (w/v) sodium chloride, and two non-