Stability of lyophilized Oxaliplatin formulation in polyolefin infusion bags containing 5% dextrose injection

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Abstract

Background:

Available data regarding the in-use stability of oxaliplatin solutions are based only on 5mg/ml aqueous concentrate formulation.

Objective

The in-use stability of lyophilized oxaliplatin and lactose formulation diluted in 5% dextrose injection was studied to assess the feasibility of preparing Oxaliplatin solutions in advance in hospital pharmacy settings.

Methods:

Oxaliplatin solutions of 0.5 mg/ml (n=6), 0.7 mg/ml (n=6) and 5 mg/ml (n=6) were prepared, using oxaliplatin 100 mg powder, and 100 ml of 5% dextrose injection in polyolefin infusion bags. The samples were stored at 2°-8 °C without light protection and analyzed at 1, 2, 4, 7, 14, 21 and 60 days. All preparations were manipulated and tested according to the Ph. Eur. The in-use stability was studied using the HPLC stability indicating method for detection of oxaliplatin concentration and degradation products. The solutions were checked for color, particulate matter and pH.

Results:

The mean concentrations of 0.5 mg/ml and 0.7 mg/ml oxaliplatin solutions in 5% dextrose injection decreased, within 7 and 14 days respectively, to less than 90% compared with the initial drug concentration in the solutions. The concentrated solution of 5 mg/ml oxaliplatin in 5% dextrose injection in infusion bags was stable (over 90%) for at least 60 days. The color, clarity and pH remained unchanged throughout the storage period. Sterility and apirogenicity standards were met as defined in the Ph. Eur.

Conclusion:

Lyophilized infusion solutions of Oxaliplatin 100 mg, 0.5 mg/ml and 0.7 mg/ml stored in polyolefin infusion bags, were chemically unstable within 7 days and 14 days respectively, at 2°-8°C without light protection. 5 mg/ml oxaliplatin in infusion bags containing 5% dextrose injection was stable for at least 60 days in the same conditions. The poor stability of diluted solutions does not allow oxaliplatin to be prepared in advance and stored in pharmacy departments.

Introduction:

Oxaliplatin is a third generation platinum analogue approved for the treatment of adjuvant and metastatic colorectal cancer[1,2]. Several publications have recently shown that diluted solutions of 5mg/ml oxaliplatin aqueous concentrate in 5% dextrose injection are stable for at least 14, 30 and 90 days in polyolefin bags under refrigeration or at room temperature without controlled light exposure[3,4,5]. Nevertheless, the manufacturers still declare chemical and physical in-use stability of 24 to 48 hours under refrigeration (2–8°C)[1,2] for both the concentrate solution and lyophilized oxaliplatin formulations.

When formulating sterile preparations for patients in hospital pharmacies, several aspects are taken into account, including dose accuracy, sterility assurance, contamination safety and stability under practical clinical conditions. An assessment of the in-use stability of the preparations is necessary for their correct storage over time[6]. The preparation of hospital batches allows for safer, more flexible and cost-effective use of the drugs, and permits quality control and end-product testing in healthcare settings[7].

The purpose of this study was to assess the in-use stability of lyophilized Oxaliplatin in 5% dextrose injection polyolefin infusion bags stored at 2°C to 8°C without light protection. The chemical and physical stability was evaluated by simulating the operating conditions of use and storage.

Methods:

Materials and Preparation of solutions.

Oxaliplatin 100 mg powder for solution in infusion vials (Mylan generics) were reconstituted with 20 ml of 5% dextrose injection to the required concentration of 5 mg/ml. A total of 18 oxaliplatin solutions were prepared at three different concentrations, commonly used in clinical practice: 0.5 mg/ml (n=6), 0.7 mg/ml (n=6) and 5 mg/ml (n=6), in polyolefin infusion bags containing 5% dextrose injection. During the study, additional 0.5 mg/ml (n=3) and 0.7 mg/ml (n=3) oxaliplatin solutions were prepared using Eloxatin 100 mg powder for solution in infusion vials (Sanofi-Aventis). The containers consisted of Baxter Viaflo polyolefin infusion bags containing 100 ml of 5% dextrose injection. All formulations were prepared under laminar flow in a safety cabinet, in accordance with the sterile preparation requirements for cytotoxic injectable drugs in microbiologically validated environments. The samples were also tested for microbiological contamination according to the Ph. Eur[8]. Sterility and apirogenicity were tested by simulating critical manipulation during drug preparation and subsequent storage, using both sterile apirogen 5% dextrose injection and Tryptone Soya Broth, a nutrient medium.

These solutions were stored in a refrigerator (2°C to 8 °C) without light protection.

The chromatograms were obtained using HPLC Agilent including Chemstation for LC 3D systems and a UV-VIS Diode Array detector set at 205 nm and 255 nm. The HPLC method was adopted for use in this study from the European Pharmacopoeia oxaliplatin monograph regarding the detection of impurities[9]. Oxaliplatin and its degradation products were separated isocratically on reverse phase analytical column Agilent Zorbax SB C18 column (5 µm, 4.6x250 mm) with the C18 pre-column at room temperature. The mobile phase was prepared by mixing monobasic sodium phosphate and phosphate acid in HPLC grade water. The 0.002 M buffer solution was adjusted to pH 3.5 with 1N hydrochloric acid and mixed with Acetonitrile (99:1 v/v). The flow rate was set at 1.3 ml/min.

Stability analysis.

Evaluation of physical and chemical stability was carried out on days 1, 2, 4, 7, 14 and 21. The stability of oxaliplatin solutions was assessed by visual examination of color and the presence of visible particles, and pH values were measured by digital pH meter* on days 1, 7 and 21. For each assay, standard solutions were prepared by reconstituting and diluting oxaliplatin vials in 5% dextrose injection to concentrations of 70, 50, 25 and 12.5 µg/ml. The standard curve was obtained by plotting the oxaliplatin concentration against peak area, with a good correlation $R^2 \geq 0.99$. This was used to calculate drug concentrations in the samples. Samples of each solution were transferred into 150 µl vials and diluted to a nominal oxaliplatin concentration of 50 µg/ml with 5% dextrose injection. The analysis was performed within 10 minutes of dilution of the samples. Duplicate HPLC determinations were performed on each of the six samples for a total of twelve assays for each concentration.

The HPLC method was validated for stability by accelerated degradation[10]. According to this method, intact oxaliplatin 50 µg/ml sample was eluted at 5.8 minutes with peak area of 247.4 (Figure 1). Oxaliplatin 50 µg/ml was exposed to 6 N hydrochloric acid, and after 90 minutes the intact oxaliplatin peak decreased to less than 50% of the initial value. Oxaliplatin 50 µg/ml was also exposed to 5 N sodium hydroxide and within 90 minutes there was a 50% loss of intact oxaliplatin peak and a new peak eluted at about 2.2 minutes. Incubation with 3% hydrogen peroxide destroyed about 20% of intact oxaliplatin peak in 20 minutes and a new peak was observed, eluting at 2.4 minutes. In addition, degradation was forced by heating oxaliplatin 50 µg/ml, and after 120 minutes more than 50% was destroyed (Figure 2).

The initial concentrations of oxaliplatin in the samples were defined as 100%. The sample concentrations were expressed as a percentage of initial concentrations at each time interval. Stability was defined as not less than 90% of the initial drug concentration remaining in the solutions[10].

Results

Oxaliplatin powder for 100 mg infusion solution, diluted in 5% dextrose injection to 0.5 mg/ml and 0.7 mg/ml and stored in polyolefin infusion bags, was chemically instable within 7 days and 14 days, respectively, at 2°-8°C without light protection (Table 1).

The mean concentration of 0.5 mg/ml oxaliplatin solution decreased to 88.7% at day 7 compared with the initial drug concentration. The mean concentration of 0.7 mg/ml oxaliplatin solution also decreased to 89.8% at day 14 and 87.9 % at day 21 of the initial drug concentration. On the other hand, lyophilized oxaliplatin reconstituted with 5% dextrose injection to the concentration of 5 mg/ml and stored in polyolefin infusion bags was stable within 21 days in the refrigerator without light protection. For this reason, the storage period was extended in time, and after 60 days 5mg/ml concentrated solution retained 96.8% of the initial drug concentration (Table 2).

A chromatographic analysis of the infusion samples showed minor peaks over the study period, but no major degradation was observed. The total of all unspecified impurities was less than 1% of the main compound at each time interval[11]. The decrease in oxaliplatin peak area was used to evaluate degradation of oxaliplatin solution samples.

All tested solutions were physically stable: clear, colorless, without precipitates, and the pH value remained unchanged over the whole storage period. From the microbiological point of view, sterility and apirogenicity conditions were met as defined in the Ph. Eur: 18 bags containing 5% dextrose injection were sterile, LAL test < 0.5 EU/ml.

Discussion:

This study examined oxaliplatin, which was supplied as sterile, preservative free lyophilized powder for reconstitution and dilution in 5% dextrose injection. Lactose monohydrate was present as an inactive ingredient at 900mg in 100 mg dosage strength.

Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with oxalate ligand as a leaving group. Oxaliplatin is known to undergo oxidative degradation in aqueous solution with the formation of Pt(DACH) complexes[12]. These reactions are time-dependent and proceed slowly in 5% dextrose injection. The degradation of oxaliplatin in aqueous solution is accelerated by adding sodium hydroxide, as demonstrated in our indication of stability test, but it rarely causes a risk of instability in a clinical environment[13]. The common error in hospitals is for oxaliplatin to be reconstituted and diluted with 0.9% sodium chloride solution, which leads oxaliplatin to decompose rapidly into the metal complex and a precipitate to form[14].

Sanofi-Aventis has recently reported that the addition of reducing sugars, such as lactose monohydrate, at a concentration of 5% w/v into aqueous solutions of 5 mg/ml oxaliplatin, result in the formation of new Pt(DACH) complexes at significant levels; the Total Chromatographic Impurity is 2-3 times greater[11,15]. These new Pt(DACH) species were not found in the 5 mg/ml oxaliplatin in water solution, with no added sugar, which was used as a control for this study.

The medicinal products prepared in advance offer many advantages in terms of improved safety by reducing errors in preparation and offering Quality Control on the finished product. Batch preparation increases the efficiency of pharmacy services by optimizing the workload and reducing waste. However, an evaluation of the in-use stability of the preparations is necessary for their correct storage over time. Several available guidelines, such as the ICH, EMEA and EU Pharmacopoeia monographs, are extremely useful, but they have not been designed specifically to challenge practical conditions in healthcare settings. "PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments" (PIC/S PE 010-3, 2008) sets specific standards for small-scale batch productions by hospital pharmacies for direct patient supply, in which the principles of GMP have been applied to hospital pharmacy preparations (PIC/S PE 009)[16].

Conclusion:

Our data clearly show the importance of the chosen oxaliplatin formulation type, aqueous concentrate or lyophilized powder containing lactose, on the chemical stability of infusion preparations. Lyophilized oxaliplatin 100 mg diluted in 5% dextrose injection to 0.5 mg/ml and 0.7 mg/ml and stored in polyolefin infusion bags were chemically unstable within 7 and 14 days, respectively, at 2°C-8°C without light protection. Reconstituted oxaliplatin as 5 mg/ml in infusion bags containing 5% dextrose injection was stable for at least 60 days, when stored at 2-8°C without light protection. The poor stability of diluted solutions means that oxaliplatin cannot be prepared in advance and stored in pharmacy departments. However, concentrated oxaliplatin solution bags may be considered for long-term storage.

Table.1 Stability of Oxaliplatin 0.5 and 0.7 mg/ml in polyolefin infusion bags containing 5% dextrose injection at 2°-8°C/light

	% Initial Concentration Remaining (Mean±SD), 95% CI					
Concentration	**Initial conc (µg/ml)**	**Day 1**	**Day 4**	**Day 7**	**Day 14**	**Day 21**
Oxaliplatin 0.5 mg/ml	50.98 +/- 1.47 95% CI [49.43;52.52]	101.96+/-2.95 95% CI [98.86;105.06	90.86+/-1.96 95% CI [88.80;92.91]	88.74+/-1.86 95% CI [86.78;90.69]	88.67+/-2.62 95% CI 85.92;91.42]	86.62+/-2.15 95% CI84.36;88.87]
Oxaliplatin 0.7 mg/ml	68.59 +/- 1.67 95% CI [66.84;70.34]	97.99+/-2.37 95% CI [95.50;105.48]	95.13+/-4.35 95% CI [90.56;99.70]	91.99+/-6.56 95% CI [85,11;98.87]	89.87+/-1.62 95% CI [88.17;91.57]	87.95+/-0.68 95% CI [87.24;88.64]

Table.2 Stability of Oxaliplatin 5 mg/ml in polyolefin infusion bags containing 5% dextrose injection at 2°-8°C/light

% Initial Concentration Remaining (Mean±SD), 95% CI							
Initial conc (µg/ml)	**Day 1**	**Day 4**	**Day 7**	**Day 14**	**Day 21**	**Day 42**	**Day 60**
47.00 +/- 0.56 95% CI [46.41;47.58]	97.27+/- 2.72 95% CI [90.62;96.33]	96.48+/- 2.25 95% CI [95.52;100.25]	97.89+/- 2.25 95% CI[95.52;100.25]	97.60+/- 1.43 95% CI [96.09;99.10]	97.27+/- 2.72 95% CI [90.62;96.33]	97.83+/- 2.00 95% CI [95.73;99.93]	96.88+/- 1.82 95% CI[94.97;98.79]

Conflict of interest statement

NONE

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Figure 1. Standard Eloxatin 50 µg/ml, peak area 247.4, time 5.76 min

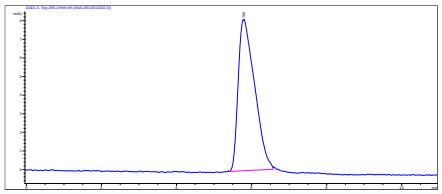
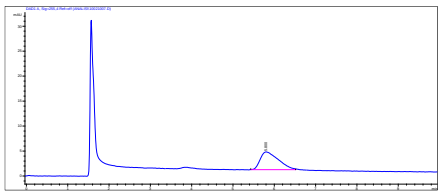
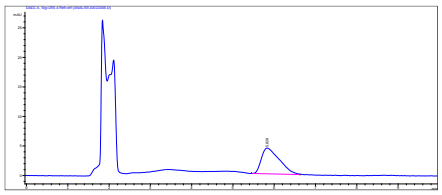


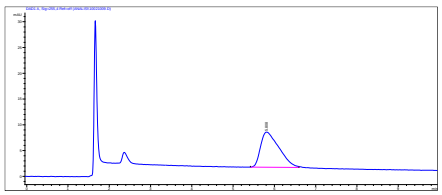
Figure 2. Oxaliplatin 50 µg/ml exposed to HCl 6 N within 90 min peak area 107.6, time 5.8 min



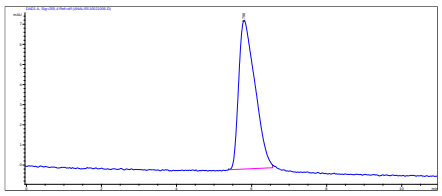
Oxaliplatin 50 µg/ml exposed to NaOH 5 N within 90 min peak area 131.3, time 5.8 min



Oxaliplatin 50 µg/ml exposed to H2O2 5 N within 90 min peak area 210.6, time 5.8 min



Oxaliplatin 5 mg/ml heated to 60°C then diluted to 50 µg/ml , within 90 min peak area 223.4 time 5.8 min



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