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experts in parenteral chemical & biological drug stability testing

Extension of the practical shelf life of hazardous drugs using the Tevadaptor® closed system transfer device (CSTD) as a container system for preservative free single use vials for up to 28 days.

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Introduction

Closed system transfer devices (CSTD) are designed to protect operators handling hazardous drugs and minimise the risk of microbiological contamination [1].

This study tests whether the **Tevadaptor® CSTD** (Figure 1) can be used to extend practical shelf life of drugs by maintaining microbiological and physicochemical integrity when multiple withdrawals are made from non preserved single use drug vials.

Figure 1. This shows the Tevadaptor vial adaptor being fitted to a glass vial.

Figure 2. This shows the push and click ease of use when attaching a Tevadaptor syringe adaptor to the vial adaptor for making a withdraw from the vial.

With the increasing pressure on hospitals to reduce the drug cost burden, the hospital pharmacist is challenged with identifying means to reduce drug wastage, without impacting drug safety or efficacy [2]. The data presented in this study may be used by the pharmacist to help support the decision to extend the practical in-use shelf life of drug products when used with the **Tevadaptor®** system.

Maintenance of a Sterile Barrier

- **Tevadaptor® Vial Adaptor** (Figure 1) was fitted onto 100 mL type 1 glass vials containing 50 ml sterile TSB growth medium (n=332). Aliquots (5 mL) were withdrawn from each vial on days 0, 7, 14 and 28 (n=332) by attaching a **Tevadaptor® Syringe Adaptor** (Figure 2) onto the vial adaptor and using a 5 mL sterile syringe to withdraw 5mL of growth medium. All manipulations were performed in an ISO class V environment. Syringes were capped, incubated for 14 days at 30 – 35±1°C and inspected for signs of microbial growth.
- Following withdrawal of the final sample on day 28, the vial containing the remaining growth medium (10 mL) was incubated for 14 days at 30 – 35±1°C and then examined for microbial growth. No signs of microbial growth were observed in any of the samples withdrawn during the 28 day test period or in the growth media remaining in the vial (Table 1). The growth promoting capability of the medium used in the study was verified by performing growth promotion testing (GPT) against a panel of ATCC microbiological organisms (positive controls).

Table 1. Sterility Testing of Vial and **Tevadaptor® System** Components During 28 Days Simulated Usage.

Sample time point (n = 5)	Container type and number tested for sterility after sample withdrawal	Result (following 14 days incubation at 30 – 35±1°C)
zero	5mL Syringe (n=332)	No growth observed
7 days	5mL Syringe (n=332)	No growth observed
14 days	5mL Syringe (n=332)	No growth observed
21 days	5mL Syringe (n=332)	No growth observed
28 days	5mL Syringe (n=332)	No growth observed
28 days	Residual TSB in Type I glass drug vial (n=332)*	No growth observed
Positive Control**		Growth observed with all microbial strains

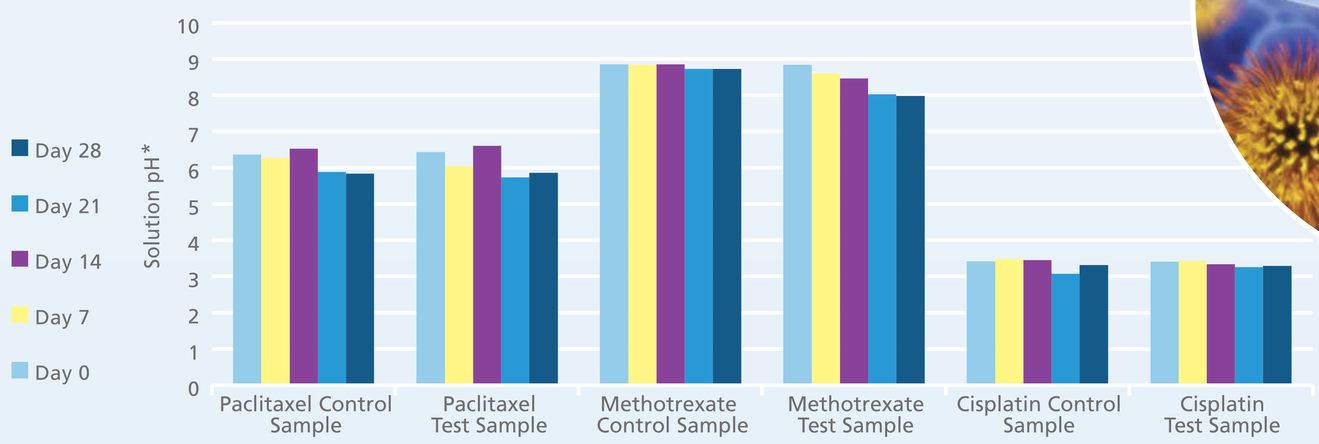
* Following withdrawal of the 28 day sample, the drug vials containing residual TSB were tested for sterility by incubating them for 14 days at 30 – 35±1°C and then examining them for microbial growth.

**Following the 14 day incubation the growth promoting capability of the media was confirmed by inoculation of sample aliquots with <100 colony forming units of 2 microbial strains and 2 fungal strains of microorganisms, as defined in the British Pharmacopoeia.

In–use Physicochemical Stability of three cytotoxic drugs

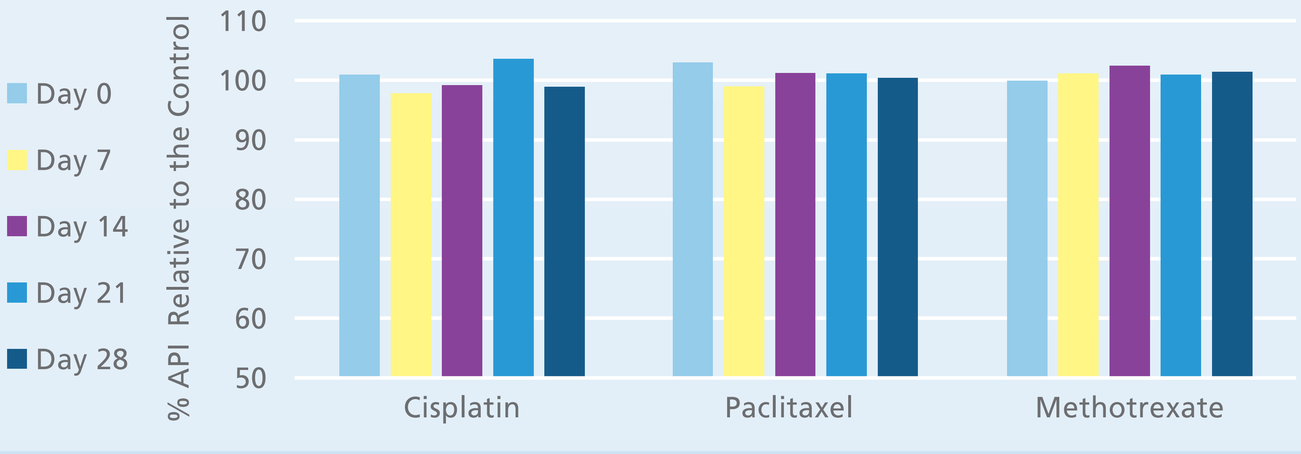
- The physicochemical stability of three antineoplastic drugs; cisplatin (1mg/mL, 100 mL vial), methotrexate (25 mg/mL, 40 mL vial) and paclitaxel (6 mg/mL, 50 mL vial), was evaluated, with the **Tevadaptor® Vial Adaptor** attached to the test vials, over a 28 day in-use period.
- Samples were withdrawn and tested on days 0, 7 14, 21 and 28. Results for the **Tevadaptor® Vial Adaptor** test samples were compared to freshly prepared control samples withdrawn using a disposable syringe and needle.
- A range of analytical techniques were setup and validated to provide assurance of the physicochemical properties of cisplatin, paclitaxel and methotrexate. **These included:**
  - **Visual inspection – appearance** of the drug solution was monitored using white fluorescent light against black and white backgrounds to detect visible particles and changes in colour and clarity.
  - **pH determination – pH** was measured with a glass combination electrode to determine pH changes which may lead to drug degradation. See Table 2.
  - **High Performance Liquid Chromatography (HPLC) –** used to evaluate the **chemical integrity** of drug active pharmaceutical ingredient. For each drug a stability indicating HPLC method was developed based on a known published method [3, 4, 5]. Each of the methods was validated prior to use. See Table 3.
- The physicochemical stability test results for pH and HPLC are presented in Table 2 and Table 3.
- Solution Clarity, Color and Absence of Particulates was determined during storage. For all three drugs, no changes in solution color or clarity were observed. All test samples were found to be free of visible particles.

Table 2. pH results for In-use Stability Testing, Day 0, 7, 14, 21 & 28.



*Average of two measurements

Table 3. Results of the analysis of drug % API in the Tevadaptor Test Samples Relative to the Control.



Bar graphs representing API content in test vials with the Tevadaptor relative to freshly prepared control samples. Content was measured using a validated stability indicating method and was based on the area of the main peak. The acceptance criteria were for the relative difference between the main peak of the Test sample and freshly prepared control sample to be less than 10% and for the Test and control chromatograms to be visually comparable.

Conclusions

Sterility testing of multiple drug vials (n=332) confirmed that sterility was maintained throughout the 28 daytest period and the following 14 day incubation period. The sterile barrier remained intact in the drug vials fitted with the Tevadaptor® system, even when challenged with multiple withdrawals from the preservative free test vials over the 28 day test period.

In all of the physicochemical tests conducted for cisplatin and paclitaxel, the samples withdrawn using the Tevadaptor® system behaved analogously to the control samples withdrawn using a standard syringe and needle. There was no evidence for drug degradation or loss of integrity over the 28 day test period.

With methotrexate there were no changes in the HPLC profile or in the appearance of the Tevadaptor® samples relative to the control samples. A slight negative drift in pH was observed in both sets of samples, with a slightly higher drift in the Tevadaptor® Test samples relative to the control samples, however within the USP acceptance criteria for pH.

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