

Stability of Ertapenem 100 mg/mL in Manufacturer's Glass Vials or Syringes at 4°C and 23°C

Scott E Walker, Shirley Law, William Perks, and John Iazzetta

ABSTRACT

Background: Prophylactic administration of ertapenem as a single 1-g IV dose has been shown to reduce sepsis after prostate biopsy.

Objective: To evaluate the stability of ertapenem after reconstitution with 0.9% sodium chloride to a final concentration of 100 mg/mL and storage in the manufacturer's original glass vials or polypropylene syringes.

Methods: On study day 0, 100 mg/mL solutions of ertapenem were retained in the manufacturer's glass vials or packaged in polypropylene syringes and stored at 4°C or 23°C without protection from fluorescent room light. Samples were assayed periodically over 18 days using a validated, stability-indicating liquid chromatographic method with ultraviolet detection. A beyond-use date was determined as the time for the concentration to decline to 90% of the initial (day 0) concentration, based on the fastest degradation rate, with 95% confidence.

Results: Reconstituted solutions stored in the manufacturer's glass vials or polypropylene syringes exhibited a first-order degradation rate, such that 10% of the initial concentration was lost in the first 2.5 days when stored at 4°C or within the first 6.75 h when stored at room temperature (23°C). Analysis of variance showed differences in the percentage remaining due to temperature ($p < 0.001$) and study day ($p < 0.001$) but not type of container ($p = 0.98$). When a 95% CI for the degradation rate was calculated and used to determine a beyond-use date, it was established that more than 90% of the initial concentration would remain for 2.35 days at 4°C and for 0.23 day (about 5 h, 30 min) at room temperature.

Conclusions: A 100 mg/mL ertapenem solution stored in the manufacturer's glass vial or a polypropylene syringe will retain more than 90.5% of the initial concentration when stored for 48 h at 4°C and for an additional 1 h at 23°C.

Key Words: ertapenem, stability, polypropylene syringes, high-performance liquid chromatography

RÉSUMÉ

Contexte : Il a été démontré que l'administration prophylactique d'une dose unique de 1 g d'ertapénem par voie intraveineuse réduit les risques de sepsis après une biopsie de la prostate.

Objectif : Évaluer la stabilité de l'ertapénem reconstitué avec une solution de chlorure de sodium à 0,9 % pour atteindre une concentration finale de 100 mg/mL et placé dans les fioles de verre d'origine du fabricant ou dans des seringues de polypropylène.

Méthodes : Au jour 0 de l'étude, des solutions de 100 mg/mL d'ertapénem ont été conservées dans les fioles de verre d'origine du fabricant ou conditionnées dans des seringues de polypropylène. Elles ont ensuite été entreposées à des températures de 4 °C ou de 23 °C sans protection contre la lumière des lampes fluorescentes de la pièce. Les échantillons ont été dosés périodiquement pendant 18 jours à l'aide d'une épreuve validée mesurant la stabilité par chromatographie liquide avec détection ultraviolette. Une date limite d'utilisation a été établie comme étant le temps nécessaire pour atteindre 90 % de la concentration initiale (jour 0), et ce, en fonction du taux de dégradation le plus rapide, avec un niveau de confiance de 95 %.

Résultats : Les solutions reconstituées placées dans les fioles de verre du fabricant ou dans les seringues de polypropylène ont présenté un taux de dégradation de premier ordre, de sorte que la concentration initiale avait chuté de 10 % après les 2,5 premiers jours d'entreposage à 4 °C ou après les 6,75 premières heures d'entreposage à température ambiante (23 °C). L'analyse de variance a montré des différences dans le pourcentage restant qui étaient associées à la température ($p < 0,001$) et au jour de l'étude ($p < 0,001$), mais pas au type de contenant ($p = 0,98$). Lorsqu'un intervalle de confiance de 95 % pour le taux de dégradation a été calculé et utilisé pour déterminer la date limite d'utilisation, on a établi qu'il resterait plus de 90 % de la concentration initiale pendant 2,35 jours à 4 °C et pendant 0,23 jour (environ 5 heures 30 minutes) à température ambiante.

Conclusions : Une solution de 100 mg/mL d'ertapénem placée dans la fiole de verre du fabricant ou dans une seringue de polypropylène conserve plus de 90,5 % de sa concentration initiale après avoir été entreposée pendant 48 heures à 4 °C et pendant 1 heure additionnelle lorsqu'elle est entreposée à 23 °C.

Mots clés : ertapénem, stabilité, seringues de polypropylène, chromatographie liquide haute performance

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INTRODUCTION

The beyond-use date for IV medications following reconstitution or dilution is often limited because of the potential for breaks in sterility. However, when reconstitution and dilution are carried out in a sterile environment, following USP Chapter <797> recommendations,¹ it is entirely reasonable to extend the beyond-use dates of these products beyond 24 h.¹ Extending the beyond-use date may reduce wastage of many drugs.^{2,3}

Antibiotic prophylaxis before transrectal biopsy of the prostate reduces the incidence of subsequent urosepsis and improves patient outcomes. However, the usual agents (e.g., ciprofloxacin) are not reliably active against the gram-negative organisms encountered in this setting. Losco and others⁴ have reported that a single 1-g dose of ertapenem is effective in improving outcomes after transrectal biopsy of the prostate. Ertapenem has advantages over meropenem because it has a longer half-life and can be administered as a single dose before the procedure. These characteristics also make ertapenem a potential option for outpatient parenteral antimicrobial therapy for the treatment of infections, a situation in which once-daily parenteral administration is an advantage.⁵

Previous studies of ertapenem stability have evaluated concentrations of 10 and 20 mg/mL following reconstitution and dilution in various IV infusion solutions and storage in various types of container.^{6,7} However, Sajonz and others⁸ have reported that the degradation rate of ertapenem is concentration-dependent, and Walker and others⁹ and Manning and others¹⁰ have reported that the stability of another carbapenem, meropenem, is also concentration-dependent. As such, it is apparent that the stability results of Phipps and others⁶ and McQuade and others⁷ should not be extrapolated, and that the stability of ertapenem at a concentration of 100 mg/mL should be directly evaluated. The current Canadian product monograph for ertapenem (Invanz) states that the reconstituted solution (with a concentration of 100 mg/mL) should be used within 6 h following preparation.¹¹ Jain and others¹² recently published their evaluation of the stability of a 100 mg/mL solution, indicating that at room temperature, the reconstituted 100 mg/mL solution declines to 87.8% of the initial concentration within 1 h. The data of Jain and others¹² demand that each dose be freshly reconstituted, which would strongly affect the ability to deliver treatment in a clinic setting⁴ or as outpatient therapy.⁵ Therefore, the recommendations of the product monograph¹¹ and of Jain and others¹² must be reconciled so that patients are not placed at risk.

The objective of this study was to evaluate the stability of a 100 mg/mL solution of ertapenem stored in either the manufacturer's original glass vials or polypropylene syringes at either 4°C or room temperature (23°C) over 18 days. During the 18-day study period, the drug concentration was determined on a total of 8 study days (days 0, 1, 2, 4, 7, 11, 14, and 18). On each study

day, each solution was also inspected visually for physical characteristics (e.g., particulate matter, colour).

METHODS

Liquid Chromatographic Method

A liquid chromatographic stability-indicating method was developed and validated.¹³⁻¹⁵ The liquid chromatographic system consisted of a solvent delivery pump (model P4000, Thermo Separation Products, Fremont, California), which pumped a mixture of 50% acetonitrile and 50% 0.05 mol/L potassium phosphate (HPLC-grade, catalogue number P286-1, Fisher Scientific, Fair Lawn, New Jersey) through a 15 cm × 4.6 mm reversed-phase C-18, 3- μ m column (Supelcosil ABZ+, Sigma-Aldrich, Oakville, Ontario) at 1.0 mL/min. The pH of the buffer was adjusted to 3.2 with concentrated phosphoric acid (HPLC-grade, catalogue number P286-1, Fisher Scientific, Fair Lawn, New Jersey) before mixing with acetonitrile. On each day, the strength of the mobile phase was prepared to achieve a retention time for ertapenem of about 4.5 min. Five microlitres of each prepared sample, quality control sample, or standard was injected directly onto the liquid chromatographic column using an autoinjector (Ultra WISP 715, Waters Scientific, Toronto, Ontario) in duplicate.

The column effluent was monitored with a variable-wavelength ultraviolet detector (UV6000, Thermo Separation Products, Fremont, California) set at 226 nm. The signal from the detector was integrated and recorded with a chromatography data system (ChromQuest, version 5.0, Thermo Fisher Scientific Inc, Nepean, Ontario). The area under the ertapenem peak at 226 nm was subjected to least-squares linear regression, and the actual ertapenem concentration in each sample was determined by interpolation from the standard curve.

Assay Validation

Following set-up of the chromatographic system for ertapenem, the suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of ertapenem with heat. A 4-mg reference standard of ertapenem (Merck Canada, Kirkland, Quebec; lot EB015A0) was dissolved in 10 mL of distilled water to prepare a 0.40 mg/mL solution. This solution was sampled and then incubated in a water bath at 80°C for 254 min. Samples were drawn and the ertapenem concentration was determined at 15, 38, 80, 100, 135, 200, and 254 minutes. The degradation study was stopped at 254 min, when only 15.83% of the initial ertapenem concentration remained. Chromatograms from all samples were inspected for the appearance of additional peaks, and the ertapenem peak was compared between samples for changes in concentration, retention time, and peak shape (by means of electronic overlay and numeric calculation of tailing). The UV spectral purity of the ertapenem peak in a chromatogram of a degraded sample

was determined by means of the UV6000 variable-wavelength ultraviolet detector (200–365 nm, 6-nm bandwidth, deuterium lamp) and compared with the spectrum of the authentic, undegraded standard of ertapenem in water obtained at time 0.

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days,¹⁶ and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.

Stability Study

On study day 0, twelve 1000-mg vials of ertapenem (Invanz, Merck Canada; lot 2106970, expiry July 2015) were each reconstituted according to the manufacturer's instructions with 10 mL of 0.9% sodium chloride to prepare 100 mg/mL solutions. The contents of 6 vials were individually drawn into 10-mL polypropylene syringes; the contents of the other 6 vials were retained in the original glass containers. Three of the original manufacturer's glass vials and 3 syringes were stored at room temperature (23°C), without protection from fluorescent room light; the other 3 glass vials and the other 3 syringes were stored in the refrigerator (4°C).

Physical Stability

On study days 0, 1, 2, 4, 7, 11, 14, and 18, samples were drawn from each container for concentration analysis, and were inspected visually against a white and a black background for changes in colour and presence of particulate matter.

Ertapenem Analysis

On each study day (days 0, 1, 2, 4, 7, 11, 14, and 18), 10 mg of a reference standard of ertapenem (Merck Canada; lot EB015A0) was dissolved in 10 mL of distilled water to make a 1.0 mg/mL stock solution. This solution was further diluted to prepare standards with final concentrations of 0.750, 0.375, 0.1875, and 0.09375 mg/mL. When combined with a blank, these standards served to construct a standard curve. In addition, 3 quality control samples with ertapenem concentrations of 0.50, 0.25, and 0.125 mg/mL were prepared from a second weight of the reference standard. Five microlitres of each standard, sample, or quality control sample was chromatographed in duplicate. Intra- and inter-day errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

On each study day (days 0, 1, 2, 4, 7, 11, 14, and 18), samples drawn from each of the 3 vials and 3 syringes stored at each temperature were assayed for ertapenem content. All samples initially contained a nominal concentration of 100 mg/mL of ertapenem. A 0.5-mL volume of each sample was diluted to 100 mL with distilled water. After thorough mixing of the sample, 5 µL of each sample was injected directly onto the

liquid chromatographic system, in duplicate, to ensure the ability to distinguish concentrations in each vial that differed by at least 10%.^{17,18}

Data Reduction and Statistical Analysis

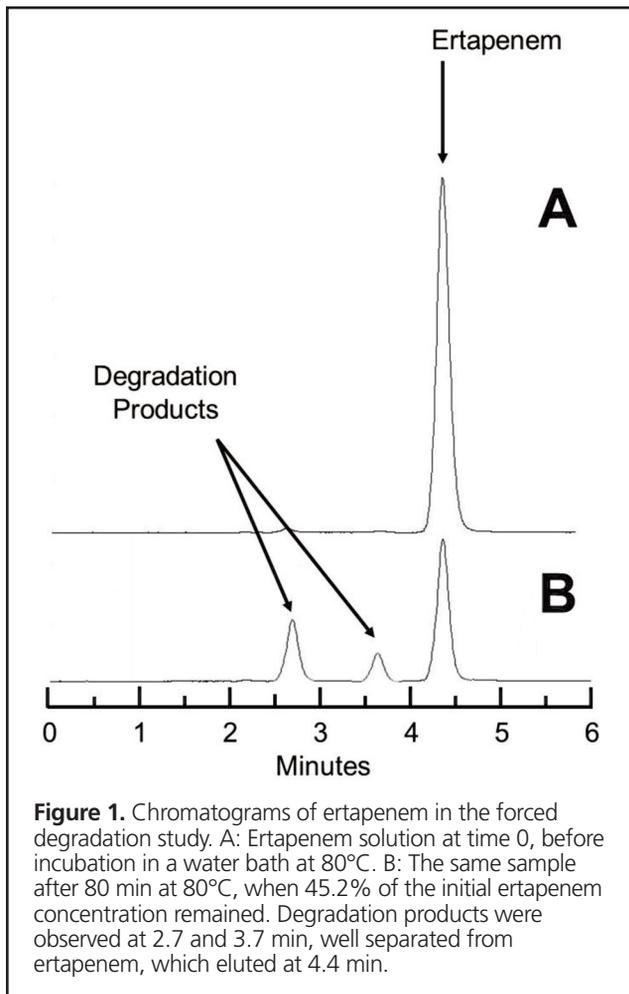
After determination of the coefficient of variation of the assay, a power calculation showed that analysis of duplicate samples had the ability to distinguish between concentrations that differed by at least 10% within each individual container.^{17,18} Means were calculated for replicate analyses. Linear regression was used to determine the change in concentration over the study period (degradation rate) for each combination of container and temperature. The 95% confidence interval (CI) of the change in concentration with time (degradation rate) was calculated for vials and syringes held at 4°C and 23°C. Analysis of variance was used to test differences in concentration on different study days, with different containers, and at different storage temperatures. The 5% level was used as the a priori cut-off for significance. Ertapenem concentrations were considered "acceptable" or "within acceptable limits" if the lower limit of 95% CI of concentration remaining was greater than 90% of the initial (day 0) concentration.

RESULTS

Accelerated Degradation and Assay Validation

Degradation of ertapenem with heat occurred relatively quickly, such that less than 16% of the initial ertapenem concentration remained after 254 min. Degradation appeared to occur in a first-order fashion, with a half-life of 1.9 h ($r = 0.9994$). As a result of the chromatographic separation of degradation products from ertapenem (Figure 1) and the similarity of the UV spectrum (200–365 nm) between a fresh ertapenem sample and the ertapenem in a degraded sample, it was concluded that this analytical method was capable of indicating stability.¹³⁻¹⁵

Analysis of accuracy and reproducibility during the study period indicated that the ertapenem concentration was measured accurately and reproducibly. Accuracy, based on the mean of duplicate determinations of standards over the study period, showed deviation of about 2% (specifically 2.06%) from the expected concentration. Analytical reproducibility within a day (as measured by the coefficient of variation) averaged 1.32% for standards and 1.07% for quality control samples. These values indicate that, with duplicate analysis, differences of 10% or more can be confidently detected with acceptable error rates.^{17,18} System suitability criteria were developed from daily calculations of theoretical plates, tailing, retention time, and observed during the validation period and were used to ensure continued chromatographic performance during the study period. On each study day, the strength of the mobile phase was prepared to ensure a retention time for ertapenem between 4.2 and 4.9 min.



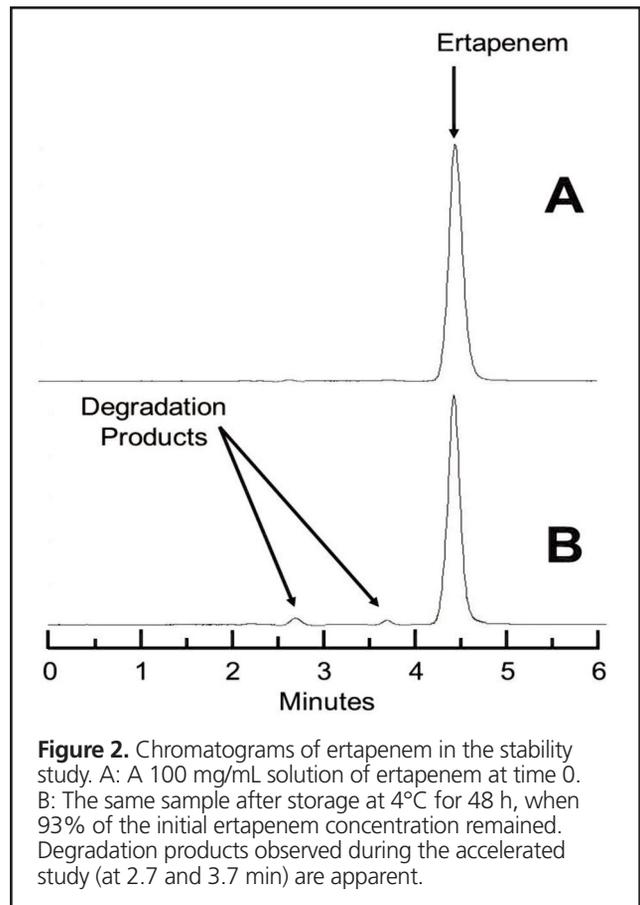
Ertapenem Stability

The initial concentration and the percentage remaining on each study day for each ertapenem storage condition are presented in Table 1.

Analysis of variance was able to detect differences in percent remaining due to temperature ($p < 0.001$) and study day ($p < 0.001$), but not type of container ($p = 0.98$). The result for temperature demonstrates that ertapenem degradation is very sensitive to changes in temperature. However, there was effectively no difference due to type of container.

Reconstituted solutions stored in the manufacturer's vials or in polypropylene syringes exhibited a first-order degradation rate, such that 10% of the original concentration was lost in the first 2.5 days with storage at 4°C or within the first 6.75 h with storage at room temperature. Degradation products were observed in study samples after storage at 4°C for 48 h (Figure 2). Degradation products from the stability study had the same retention time as those observed in the accelerated degradation study.

When a 95% CI for the degradation rate was calculated and used to determine a beyond-use date, it was established



that more than 90% of the initial concentration remained for 2.35 days at 4°C or 0.23 day (about 5 h, 30 min) at room temperature.

DISCUSSION

The stability of ertapenem was affected by temperature (with faster degradation at room temperature than at 4°C), but not type of container.

In a previous study, Phipps and others⁶ observed that during storage in an elastomeric infusion device, 10 mg/mL solutions of ertapenem in normal saline (i.e., 0.9% sodium chloride) retained 90% of the initial concentration for 5 days. McQuade and others⁷ evaluated concentrations of 10 and 20 mg/mL in a variety of IV solutions. Except for those prepared with the diluent sodium bicarbonate, solutions of 10 mg/mL retained a greater percentage of the initial concentration on all study days with storage at 5°C or 23°C relative to the 20 mg/mL solutions. Similar to Phipps and others,⁶ McQuade and others⁷ demonstrated stability of a 10 mg/mL solution of ertapenem over 5 days. This period is significantly longer than the 48 h observed for 100 mg/mL solutions in the current study. Both McQuade and others⁷ and Sajonz and others⁸ found that the degradation rate of ertapenem was concentration-dependent. Similarly,

Table 1. Percentage of Ertapenem Remaining during Storage with Refrigeration or at Room Temperature in Glass Vials or Polypropylene Syringes

Study Day	% Remaining* with Refrigeration (4°C)		% Remaining* at Room Temperature (23°C)	
	Vial	Syringe	Vial	Syringe
Initial concentration (mg/mL), day 0	105.50 ± 0.97	106.07 ± 1.03	106.38 ± 1.12	105.68 ± 1.37
1	97.16 ± 0.28	97.31 ± 0.3	975.63 ± 1.52	75.92 ± 2.45
2	92.96 ± 0.51	93.31 ± 0.95	51.43 ± 1.38	52.43 ± 1.49
4	83.49 ± 1.01	82.96 ± 0.93	22.99 ± 1.92	23.27 ± 2.17
7	71.36 ± 2.05	71.36 ± 0.63	BLOQ	BLOQ
11	62.42 ± 0.95	63.03 ± 1.00	BLOQ	BLOQ
14	56.54 ± 1.33	56.16 ± 1.02	BLOQ	BLOQ
18	48.21 ± 0.42	47.27 ± 2.00	BLOQ	BLOQ
Slope or degradation rate (1/days)†	-0.0411	-0.0418	-0.3731	-0.3698
Correlation (r)†	-0.9969	-0.9974	-0.9975	-0.9970
95% CI for slope	±0.0032	±0.0030	±0.0807	±0.0873
Fastest degradation rate (1/days), 95% CI limit‡	-0.0443	-0.0449	-0.4538	-0.4571
Shortest T-90 (based on 95% CI)§	2.38 days	2.35 days	0.23 day (5.57 h)	0.23 day (5.53 h)

BLOQ = below limit of quantitation, CI = confidence interval, SD = standard deviation, T-90 = time until 90% of original concentration remains.

*Data for percent remaining are shown as mean ± SD, where each mean is based on duplicate determination of 3 samples. The percentage remaining was calculated in relation to the amount measured on day 0 (100%).

†Calculated from log-linear regression of the percent remaining on each study day.

‡Fastest degradation rate was calculated from the lower 95% confidence limit of the degradation rate (as determined by log-linear regression) of the percent remaining on each study day.

§T-90 was calculated from the intersection of the lower 95% confidence limit and the lower limit of acceptance (90%), based on the log-linear degradation rate.

Walker and others⁹ and Manning and others¹⁰ reported that another carbapenem, meropenem, demonstrated concentration-dependent degradation in saline solutions. Therefore, it is not surprising that the current study and the study by Jain and others¹² have demonstrated significantly faster degradation rates for 100 mg/mL solutions of ertapenem.

The current Canadian product monograph for ertapenem (Invanz) states that 100 mg/mL solutions should be used within 6 h following preparation.¹¹ Jain and others¹² recently published an evaluation of the stability of a 100 mg/mL solution, reporting 12.2% loss per hour over the first hour. However, the reported rate of loss by these authors was inconsistent between test solutions and over time.¹² More specifically, the rate of loss declined dramatically with time, averaging 1.7% per hour between 4 and 24 h. A rate of loss of 1.7% per hour is consistent with the 6-h recommendation in the product monograph¹¹ and that observed in the current study.

The results presented here were analyzed on the basis of a first-order rate of loss ($r > 0.997$) because of improved prediction of the degradation rate compared with a zero-order rate of loss where correlation coefficients are slightly lower, ranging from 0.974 to 0.996 for all temperature and container combinations. The accelerated degradation study was also best fit to a first-order degradation rate (0.99 versus 0.92). This improved prediction of the degradation rate reduces error between 3- and 4.5-fold. The data of Jain and others¹² would be better fit to a first-order decline in concentration ($r = 0.972$ for first-order rate analysis, compared

with the reported zero-order rate analysis [$r = 0.930$] at 25°C). Although a first-order rate of loss cuts the error in half, the rate of loss is still inconsistent over the 24-h study period.

When the fastest first-order degradation rate, with 95% CI, is used to determine the amount remaining for a solution stored at 4°C and then removed from the refrigerator and stored at 23°C, a beyond-use-date can be calculated. For a 100 mg/mL solution (with 95% confidence) stored in the glass vial or a syringe, storage should not exceed 48 h at 4°C followed by 1 h at 23°C. Under these conditions, the drug would retain more than 90.5% of the initial concentration with 95% confidence.

CONCLUSION

Ertapenem reconstituted to a concentration of 100 mg/mL and stored in the manufacturer's original glass vials or polypropylene syringes is chemically stable for up 48 h at 4°C followed by 1 additional hour at 23°C. This level of stability may allow this drug to be prepared in advance, to optimize workload when multiple patients are scheduled for outpatient procedures requiring ertapenem for preprocedure prophylaxis.

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