Stability of meropenem in saline and dextrose solutions and compatibility with potassium chloride

Scott E Walker, Shawn Varrin, Daniel Yannicelli and Shirley Law

ABSTRACT

Objectives: *The stability and compatibility of meropenem, 50 mg and 2000 mg added to 50 mL of normal saline (NS) or 5% dextrose in water (D5W) was evaluated at -20°C and 4°C over 14 days and at 23°C over 36 hours. The stability and compatibility of meropenem in NS or D5W with potassium chloride (10 mmol/mL and 40 mmol/mL, diluted in either NS or D5W) was also evaluated at 23°C over 36 hours.*

Methods: *In addition to visual inspection and pH, the meropenem concentration of solution was determined by a stability-indicating liquid chromatographic method. Meropenem concentrations were considered acceptable if the concentration on any day of analysis was greater than 90% of the initial (day zero) concentration.*

Results: *Meropenem is more stable in NS than in D5W. The more concentrated solutions degrade faster in NS. Temperature also significantly affects stability. Solutions stored at room temperature lost more than 10% within 24 hours, while at 4°C, solutions retained 90% of the initial concentration for 1 to 7 days. At -20°C, NS solutions retained 90% of the initial concentration for at least 11 days.*

Meropenem is compatible with potassium chloride (KCl) in concentrations of 10 mmol/L and 40 mmol/L in NS and D5W at 23°C. The presence of KCl did not affect the stability of meropenem. No significant change in pH was observed during the study period.

Conclusions: *This study demonstrates that at least three factors: temperature, concentration and diluent (presence of dextrose) affect the stability of meropenem. Once reconstituted, meropenem is more stable when diluted in NS than D5W. Potassium chloride solutions are compatible with meropenem solutions and do not appear to alter the stability of meropenem.*

Key words: stability, compatibility, meropenem, potassium.chloride

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RÉSUMÉ

Objectifs : *évaluer la stabilité et la compatibilité du méropénem dans des proportions de 50 mg et 2000 mg dans 50 mL de soluté physiologique normal (NS) de dextrose à 5 % dans l'eau (D5W), à des températures de -20 °C et de 4 °C durant 14 jour et de 23 °C durant 36 heures. La stabilité et la compatibilité du méropénem dans du NS ou du D5W avec du chlorure de potassium (10 mmol/mL et40 mmol/mL, dilué dans du NS ou du D5W) ont aussi été évaluées à une température de 23 °C durant 36 heures..*

Méthodes : *Outre l'inspection visuelle et la vérification du pH, on a déterminé la concentration des solutions en méropénem, au moyen d'une épreuve destabilité par chromatographie liquide. Les concentrations en méropénem étaient considérées acceptables si à n'importe quel jour d'une analyse, elles étaient supérieures à 90 % des concentrations initiales (au jour 0).*

Résultats : *Le méropénem est plus stable dans le NS que dans le D5W. Les solutions à concentration plus élevée se dégradent plus rapidement dans le NS. La température affecte aussi grandement la stabilité. Les solutions entreposées à la température ambiante ont*

perdu plus de 10 % de leurs concentrations initiales en 24 heures, a lorsqu'entreposées à 4 °C elles ont conservé plus de 90 % de leurs concentrations initiales durant 1 à 7 jours. Les solutions de méropénem dans du NS, entreposées à 20 °C ont conservé 90 % de leur concentration initiale en méropénem pendant au moins 11 jours.

Le méropénem est compatible avec le chlorure de potassium (KCl) dans des concentrations de 10 mmol/L et de 40 mmol/L dans du NS et du D5W à 23 °C. La présence de KCl n'a pas affecté la stabilité du méropénem. Aucun changement significatif du pH n'a été observé au cours de la période d'étude.

Conclusions : *Cette étude a démontré qu'au moins trois facteurs affectent la stabilité duméropénem : la température, la concentration et le diluent (présence de dextrose). Après sa reconstitution, le méropénem est plus stable lorsqu'il est dilué dans du NS que dans du D5W. Les solutions de chlorure de potassium sont compatibles avec les solutions de méropénem et elles ne semble pas altérer la stabilité du méropénem.*

Mots clés : stabilité, compatibilité, méropénem, chlorure de potassium.

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INTRODUCTION

Pharmacists are often asked questions regarding the stability and compatibility of medications in intravenous solutions, but frequently, especially for new products, this information does not exist. When a manufacturer indicates that freshly prepared solutions must be discarded within 24 hours of preparation if they are unused, hospitals with a centralized IV additive program may waste 20% of what they prepare (due to changes in dose or discontinuation of the medication).[1] In order to reduce this waste, it is common for hospital pharmacists to extend the expiry date of an intravenous product, where stability allows.

Meropenem, is a new broad spectrum, ß-lactamase-resistant carbapenem antibiotic for parenteral administration. Prescribing information available on meropenem stability indicates that freshly reconstituted vials are stable for 2 hours when stored between 15°C and 25°C and up to 12 hours when stored at 4°C.[2] Once diluted in normal saline (NS), meropenem is stable for 4 hours at room temperature and 24 hours at 4°C. When meropenem is diluted in 5% dextrose in water (D5W), solutions are considered stable for 1 hour at room temperature and 4 hours at 4°C.2 These shelf-lives are considerably shorter than those recently reported by Patel and Cook.[3]

Therefore, the purpose of this investigation was to evaluate the chemical stability and compatibility of meropenem solutions with nominal concentrations of 1 mg/mL and 22 mg/mL, in NS or D5W at -20°C and 4°C over 14 days and at 23°C over 36 hours. The stability and compatibility of meropenem in NS or D5W with potassium chloride (10 mmol/mL and 40 mmol/mL, diluted in either NS or D5W) was evaluated at 23°C over 36 hours.

METHOD

Assay validation liquid chromatographic system

Prior to initiating this study, an analytical method developed by Zeneca Pharma Inc. and recently reported[3] was validated within our laboratory. A liquid chromatographic system consisting of a solvent delivery pump, column (C-18 reverse phase 5 mm 4.6 x 250 mm, Hypersil ODS; AllTech) and an ultra-violet detector was used. The mobile phase consisted of 1.0 M tetrabutyl amonium hydroxide, acetonitrile and methanol in a ratio of 75:15:10. The pH of the mobile phase was adjusted to 7.5 with 10% v/v phosphoric acid. The suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of meropenem with the use of heat.[4,5] Solutions of meropenem in distilled water were intentionally degraded at 2 different temperatures. Meropenem, 0.026g (meropenem trihydrate standard provided by Zeneca Pharma Inc., Bx.RS5326-245, ADM No.88059/93, Purity: 99.9%) was dissolved in 25 mL of distilled water. This solution was then placed in a glass vial and incubated in a water bath at 75°C. Samples were drawn from the vial just prior to incubation and 13 other times over a 3.25-hour period. Another meropenem trihydrate solution was made by dissolving 0.0264g of pure meropenem in 25 mL of distilled water. This solution was placed in a glass vial

and incubated in a water bath at 95°C. Samples were drawn prior to incubation and 11 other times over a 2½-hour period. Samples were chromatographed and the resulting chromatograms were inspected for the appearance of additional peaks. The meropenem peak was compared between samples for changes in concentration, retention time and peak shape.

Accuracy and reproducibility

Validation of the method, with respect to accuracy and reproducibility, was tested prior to the study period. Standard curves for meropenem consisted of 8 standards and a blank covering the range from 50% to 150% of the expected working range. However, since column and detector overload occurred at 10 mg/mL of meropenem, the highest concentration of a meropenem standard was 6 mg/mL. Therefore, to span the range of concentrations for this study, the concentration of standards ranged from 0.25 mg/mL to 6.0 mg/mL (samples in the stability portion of the study were expected to drop to at least 50% of initial; for the lowest initial concentration of 50 mg diluted in a 50 mL bag this is approximately 0.5 mg/mL). All study samples with high meropenem concentrations (2000 mg diluted in a 50 mL bag) were diluted 10-fold prior to injection to adjust the concentration within the expected range. Each sample was chromatographed in duplicate. Standards of 0.25, 0.5, 0.75, 1, 2, 4, 5 and 6 mg/mL and quality control samples of 0.3, 3 and 4 mg/mL were prepared fresh on each day to allow assessment of linearity, accuracy and reproducibility. During this evaluation period, system suitability criteria (theoretical plates, tailing and retention time) were also established for meropenem to ensure consistency between study days. Inter- and intra-day

Table I — Concentrations and solutions evaluated. KCl=potassium chloride; n/a = not available or applicable (none added); D5W = dextrose 5% in water; NS = sodium chloride 0.9% in water.

Solution number	Nominal meropenem concentration (mg/mL)	Meropenem diluent	KCl concentration (mmol/L)	KCl diluent	Temperature evaluated (°C)
Admixture					
1	1	D5W	0	n/a	-20, 4, 23
2	22	D5W	0	n/a	-20, 4, 23
3	1	NS	0	n/a	-20, 4, 23
4	22	NS	0	n/a	-20, 4, 23
Y-site simulation: concentrations mixed in equal parts					
5	1	D5W	10	D5W	23
6	22	D5W	10	D5W	23
7	1	D5W	40	D5W	23
8	22	D5W	40	D5W	23
9	1	D5W	10	NS	23
10	22	D5W	10	NS	23
11	1	D5W	40	NS	23
12	22	D5W	40	NS	23
13	1	NS	10	D5W	23
14	22	NS	10	D5W	23
15	1	NS	40	D5W	23
16	22	NS	40	D5W	23
17	1	NS	10	NS	23
18	22	NS	10	NS	23
19	1	NS	40	NS	23
20	22	NS	40	NS	23

reproducibility were assessed using the coefficient of variation (CV) of the peak area for samples determined in duplicate and accuracy was determined based on deviations from the known concentration with both standards and quality control samples.

Stability study solutions evaluated

Commercially available, sterile meropenem vials (1000 mg, Merrem®, Zeneca Pharma Inc., lot 6ZP0974, exp NOV98) were reconstituted according to the manufacturer's instructions with sterile water. Then 1 mL (50 mg) or 40 mL (2000 mg) was added to each 50 mL polyvinyl chloride minibag containing either D5W or NS.

Solutions for evaluation are identified as solution numbers 1–4 (Table I). The solutions containing 50 mg (1 mL) of meropenem added to a 50 mL bag are referred to as having a nominal concentration of 1 mg/mL and those containing 2000 mg (40 mL) added to a 50 mL bag are referred to as having a nominal concentration of 22 mg/mL. This nominal concentration does not consider PVC bag overfill or overfill in the meropenem vial. Four containers of each of the first 4 concentration-intravenous solution combinations (meropenem only in NS or D5W) were prepared and stored at either -20°C or 4°C for 14 days, simulating storage conditions encountered in routine hospital pharmacy practice. Samples were drawn immediately after the solutions had been prepared and each container was also assayed for meropenem content on days 1, 2, 3, 4, 7, 8, 9, 10, 11 and 14. On each study day, samples stored at 4°C and at -20°C from 3 of the 4 containers were prepared for chromatography and injected in duplicate. Concentrations of meropenem were interpolated from a standard and recorded to the nearest 0.01 mg/mL. On each study day the sample was also inspected visually and the pH of each solution was determined.

Experience with meropenem during the assay validation portion of the study indicated that meropenem degraded at approximately 1% per hour at room temperature. As a result it was necessary to minimize the time samples and standards were held at room temperature prior to chromatographic analysis. Therefore, samples were assayed within 1 hour of being drawn from bags stored at 4°C or removed from the freezer at -20°C and thawed at room temperature.

For solutions stored at room temperature, a single container of each concentration and solution type (solution numbers 1 through 4) was prepared. An aliquot of this solution was placed in a glass tube and the concentration of meropenem was determined chromatographically each hour for 1 mg/mL solutions and approximately 15 times over a 36 hour period for the 22 mg/mL solutions. An evaluation of the room temperature stability of each concentration and solution type study was repeated 3 times. Each sample was inspected visually and the pH of each sample was recorded immediately following preparation and at 12, 24 and 36 hours.

To simulate Y-site compatibility between meropenem and KCl, (solutions 5 through 20; Table I), the initially identified concentrations of each medication and solution type were mixed in equal parts in a glass test-tube. After mixing, each solution was observed for precipitate, colour change or evolution of gas. Visual inspection was completed at room temperature over 24 hours. Since no incompatibility was observed, a single container of each concentration and solution type was prepared. The concentration of meropenem was determined chromatographically each hour for 1 mg/mL solutions and approximately 15 times over a 36-hour period for the 22 mg/mL solutions. Each sample was also inspected visually and the pH of each sample was recorded immediately following preparation and at 12, 24 and 36 hours.

Physical inspection

Solutions drawn for the purpose of pH measurement from each storage temperature/ concentration and solution combination were removed from the PVC container and placed in clear glass test tubes to avoid misinterpretations related to the opacity of the container. Each solution was inspected visually for particulate matter against a black and a white background in diffuse laboratory light as well as for colour and clarity and the observations were recorded. For solutions stored at room temperature, this was completed immediately following preparation and at 12, 24 and 36 hours. For solutions stored at room 4°C or -20°C, physical inspection was completed on each study of the 11 study days. This inspection is only capable of detecting large visible particles. Following

inspection, the pH was determined on each of these samples.

pH

The pH of each storage temperature/ concentration and solution combination was measured to the nearest 0.001 of a pH unit. The pH meter (Accumet-model 925; Fisher Scientific, Toronto, Ontario equipped with a microprobe glass body electrode cat# 13-639-280; Fisher Scientific, Toronto, Ontario) was standardized on each study day using commercially available buffer solutions. The pH of a standard solution was recorded prior to sample analysis and on completion of sample analysis to determine if drift in pH had occurred during the analysis period.

Data reduction and statistical analysis

Means were calculated for replicated analyses and are reported in summary tables. Mean results from different days and from different solutions were compared statistically to determine if an association exists between the observed result and time through linear regression. Analysis of variance was used to test differences in degradation rate between temperature, concentration and solution combinations. Fisher's Protected Least Significant Difference Multiple Range Test was used to test the significance of individual pair-wise comparisons. The 5% level was used as the a priori cut-off for significance. Meropenem concentrations were considered acceptable or within acceptable limits if the concentration on any day of analysis was greater than 90% of the initial (day zero) concentration.

For studies completed at room temperature, data from each study were expressed as the percent of the initial (time zero) concentration, at each time point up to 36 hours. Since actual sampling times differed between studies, the degradation rate (first or zero order) observed for each of the 3 estimates for each solution and concentration combination were averaged. A "mean percent remaining" at each hour, from 0 to 36 hours, was calculated using this average degradation rate. The time for the concentration to be reduced to 90% of the initial concentration was determined by a least squared best-fit of the data. Analysis of variance was used to test differences in percent remaining between different solutions and time. Fisher's Protected Least Significant Difference Multiple Range Test was used to test the significance of individual pair-wise comparisons. The 5% level was used as the a priori cut-off for significance. Meropenem concentrations were considered acceptable or within acceptable limits if the concentration at any time was greater than 90% of the initial (time zero) concentration. A solution was judged to be acceptable or within acceptable limits if there was no visual change in the colour or clarity of the mixture and no precipitate or other particulate formation over the 36-hour period.

RESULTS

Assay validation, accelerated study

At 95°C meropenem was observed to degrade in a first order fashion (r^2= 0.9994) such that by 2 hours less than 10% of the initial meropenem concentration remained (Figure 1). At 75°C, meropenem degraded in a zero order fashion (r^2= 0.9959) and more than 60% of meropenem remained after 2 hours of incubation (Figure 1). Meropenem eluted at 4.5 minutes and 2 degradation products eluted at 6.24 and 11.36 minutes (Figure 1). During each study the size of each degradation product peak increased as the meropenem concentration declined. Neither of these degradation products interfered with meropenem quantification. As a result of the predictable degradation of meropenem and the chromatographic separation of these degradation products from meropenem, it was concluded that this analytical method was stability-indicating and capable of measuring meropenem specifically.

Validation results, accuracy and reproducibility

Based on duplicate analysis of quality control samples (concentrations of 0.30 mg/mL, 3.00 mg/mL and 4.00 mg/mL), meropenem was measured accurately with an average deviation of less than 4%. At concentrations of 3.00 and 4.00 mg/mL the deviation never exceeded 3.25%. Error (CV%) on duplicate analysis of quality control samples averaged approximately 2% within a day, and never exceeded 2.75% within a day for concentrations of 3.00 and 4.00 mg/mL. Deviation from the known concentration, for standards, averaged

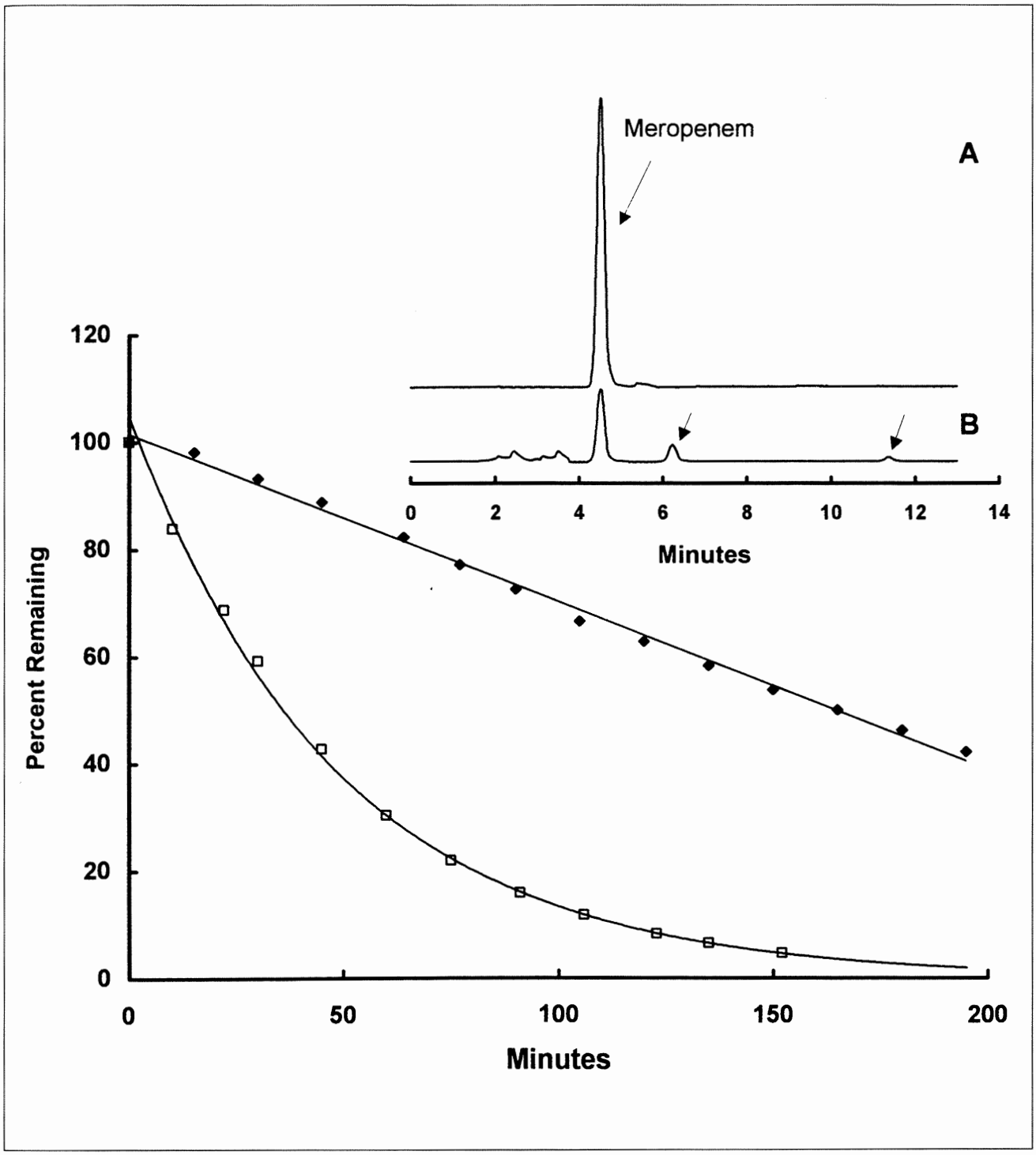

Figure 1 — Rate of loss of meropenem during the accelerated study at 95°C (open squares) and at 75°C (closed diamonds). During each study the meropenem concentration declined and degradation products were observed in chromatograms (panels A and B above). Panel A represents a chromatogram of freshly prepared meropenem at time zero and panel B represents a chromatogram of meropenem following incubation at 95°C for 60 minutes. Arrows in panel B at 6.24 minutes and 11.36 minutes include degradation products.

less than 3% and the error on duplicate analysis of standards averaged less than 2%. These analyses indicated that the meropenem concentrations were measured accurately and reproducibly and that differences of up to 10% could be confidently detected with duplicate injection.[6]

Storage at -20°C

On each study day the observed concentration of meropenem from each of 3 50 mL bags of D5W or NS containing either 50 mg or 2000 mg of meropenem was determined in duplicate and averaged. These concentrations are listed in Table II. The initial concentrations are different than the nominal concentrations of 1 mg/mL or 22 mg/mL due to minibag and meropenem vial overfill. The percent remaining on day 14, relative to the initial concentration observed on day zero, is listed in Table II. In all samples stored at -20°C, the meropenem concentration was observed to decrease (Table II). The decrease in meropenem concentration was accompanied by the appearance of degradation products in all chromatograms.

Solutions diluted in D5W degraded in a log-linear (first order) fashion. Since 10% or less of the initial concentration of meropenem was lost in NS solutions, a reaction order (first vs. zero) could not be confidently determined. At -20°C, meropenem in D5W solutions (both 1 mg/mL and 22 mg/mL of meropenem) degraded faster than solutions prepared in NS. The degradation rate of 1 mg/mL of meropenem in D5W was observed to be 3-fold faster than the 22 mg/mL concentration. Conversely, based on a zero order rate, the loss per day in the 22 mg/mL solution in NS was 0.87% per day, almost 3-fold greater than the 0.3% per day observed for the 1 mg/mL solution.

Storage in the refrigerator (temperature 4°C)

On each study day the observed concentration from each of 3 bags for each storage temperature, concentration and solution combination was determined in duplicate and averaged. These concentrations are listed in Table III. The percent remaining on day 14, relative to the initial concentration observed on day zero is also listed in Table 3. In all samples stored at 4°C, the meropenem concentration was observed to decrease (Table III). The decrease in meropenem concentration was accompanied by the appearance of degradation products in all chromatograms.

Solutions diluted in NS degraded in a zero order fashion while solutions in D5W degraded in a log-linear (first order) fashion, (Table III).

At 4°C, solutions in D5W (both 1 mg/mL and 22 mg/mL of meropenem) degraded faster than solutions in NS. The degradation rate of 1 mg/mL of meropenem in D5W was observed to be 2-fold faster than the 22 mg/mL concentration. Conversely, the loss per day in the 22 mg/mL solution in NS was 2% per day, slightly more than 2-fold greater than the 0.93% per day observed for the 1 mg/mL solution. As a result the 22-mg/mL solution achieved 90% of the initial concentration within 4 days compared to approximately 9 days for the 1 mg/mL solution.

Storage at room temperature (23°C)

The observed mean time for the meropenem concentration to reach 90% of the initial concentration during storage at room temperature can be found in Table IV (KCl – "none"). For 1 mg/mL solutions, linear regression of approximately 37 concentrations from each of 3 studies in NS and 3 studies in D5W were used to establish estimates of the degradation rate and these rates were averaged. For the 22 mg/mL solutions, each of the 15 observed concentrations in each of 3 studies in NS and three studies in D5W were subjected to least squares regression and the degradation rate was determined. Solutions in NS appeared to degrade in a zero order fashion while solutions in D5W degraded in a log-linear (first order) fashion.

In all samples, the meropenem concentration was observed to decrease and this loss of concentration was accompanied by the appearance of degradation products in all chromatograms. Meropenem prepared in D5W solutions degraded faster than solutions diluted in NS. Similar to observations made at other temperatures, in D5W the 1 mg/mL solution degraded faster than the solution containing 22 mg/mL. This concentration effect was also noted at the other temperatures (Tables II and III); however, at other temperatures in NS the concentration effect was not as dramatic and in fact was opposite, as the less concentrated solutions degraded more slowly. Based

Table II — Mean concentration of meropenem and standard deviation, at -20°C. NS=sodium chloride 0.9% in water; D5W = 5% dextrose in water.

Study day	Observed mean meropenem concentration			
	1 mg/mL* in NS	22 mg/mL† in NS	1 mg/mL* in D5W	22 mg/mL† in D5W
0	1.14 ± 0.007	27.18 ± 4.039	1.09 ± 0.062	25.25 ± 0.820
1	1.15 ± 0.014	28.05 ± 3.159	1.06 ± 0.081 [96.99%]	26.16 ± 1.061
2	1.13 ± 0.006	26.79 ± 1.141	0.94 ± 0.042	26.04 ± 1.169
3	1.13 ± 0.006	25.50 ± 0.804	0.90 ± 0.076	24.61 ± 0.749
4	1.09 ± 0.005	24.65 ± 0.693	0.72 ± 0.041	23.69 ± 0.666
7	1.10 ± 0.017	24.63 ± 0.637	0.71 ± 0.030	23.78 ± 1.028 [90.59%]
8	1.11 ± 0.008	24.69 ± 0.690	0.69 ± 0.017	23.35 ± 1.023
9	1.10 ± 0.008	24.85 ± 0.929	0.72 ± 0.041	22.91 ± 0.920
10	1.08 ± 0.024	24.37 ± 0.830	0.72 ± 0.041	23.40 ± 0.683
11	1.11 ± 0.013	24.48 ± 0.931 [91.10%]	0.62 ± 0.023	22.92 ± 0.788
14	1.10 ± 0.007	23.87 ± 0.517	0.59 ± 0.020	21.46 ± 0.742
% remaining§	96.69	88.90	54.69	81.76
Equation	$y=0.2996x+100.01$	$y=0.8745x+100.08$	$y=94.615e^{(-0.0416x)}$	$y=99.627e^{(-0.0129x)}$
Time to reach 90% of initial (days)¶	33.38	11.44	1.20	7.83
r^2 value	0.5491	0.7755	0.9116	0.9058

* 1 mg/mL represents the nominal concentration of meropenem.
† 22 mg/mL represents the nominal concentration of meropenem.
§ % remaining on Day 14 relative to Day 0 concentration, expressed as a % of initial concentration.
¶ Time to reach 90% of initial concentration determined through use of the specified equation, determined by least-squared regression of the mean concentration.

on a zero order rate, the average rate of loss in the 1 mg/mL solution in NS was 0.45% per hour compared to 0.57% per hour at 22 mg/mL.

Storage at room temperature with KCl

At room temperature, the meropenem concentration was observed to decrease in all study samples. The loss of meropenem concentration was accompanied by the appearance of degradation products in all chromatograms. The presence of potassium chloride in the solutions did not significantly affect the rate of meropenem degradation. However, as was observed in solutions containing meropenem only, diluent and meropenem concentration were strong determinants of the meropenem degradation rate. In samples prepared only with NS (both 1 mg/mL and 22 mg/mL), the meropenem concentration remained within 82% of the initial concentration over the 36-hour study period at room temperature. Therefore, when meropenem was diluted in NS, meropenem appeared to be more stable than when diluted in D5W and the meropenem concentration had less effect on the degradation rate. Samples containing any amount of D5W appeared to be less stable. The two fastest degrading solutions were prepared only in D5W (containing 50 mg per 50 mL meropenem and 10 and 40 mmol/L of KCl) and approximately 69% of the initial concentration of meropenem concentration was lost in 36 hours. Similar to observations in D5W solutions without potassium chloride, the samples containing a higher meropenem concentration appeared to degrade at a slower rate. Therefore, at all temperatures, when meropenem was diluted in D5W, the increasing amount of meropenem was associated with a slower

degradation rate. The 6 solutions in which NS was the only diluent appeared to degrade in a zero order fashion while solutions containing D5W appeared to degrade in a log-linear (apparent first order) fashion (Table 4).

pH

The initial pH of all samples ranged from 7.529 to 7.935. For samples prepared in NS, the initial pH was marginally lower (approximately 0.2 of a pH unit). Solutions stored at 4°C showed a slight reduction in pH by day 14 of 0.3 pH units or less. The pH of solutions stored at -20°C for 14 days changed by less than 0.1 of a pH unit. An increase in pH was observed for solutions stored at room temperature for 36 hours, but the increase averaged less than 0.03 of a pH unit. These minor changes in pH did not appear to bear any relationship to the degradation of meropenem in these solutions. None of the changes in pH are clinically relevant as changes of less than 0.5 of a pH unit are not generally important in practice.

Physical inspection

All samples stored at -20°C or 4°C initially clear, colourless and free of particulate matter. Samples containing 1 mg/mL of meropenem remained clear and colourless throughout the study period. However, samples containing 22 mg/mL of meropenem changed from a colourless solution to a very light yellow colour over the 14-day study period when stored at -20°C, or to a darker but still light yellow colour after 14-days storage at 4°C. Samples stored at 23°C containing 1

Table III — Mean concentration of meropenem and standard deviation, at 4°C. NS=sodium chloride 0.9% in water; D5W = 5% dextrose in water.

	Observed mean meropenem concentration			
Study day	1 mg/mL* in NS	22 mg/mL† in NS	1 mg/mL* in D5W	22 mg/mL† in D5W
0	0.98 ± 0.020	25.87 ± 0.573	0.88 ± 0.022	25.67 ± 0.443
1	0.98 ± 0.023	25.26 ± 0.049	0.87 ± 0.014	24.30 ± 0.885
2	0.98 ± 0.024	24.97 ± 0.460	0.79 ± 0.012 [89.80%]	23.35 ± 0.600 [90.96%]
3	0.96 ± 0.031	24.87 ± 0.317	0.72 ± 0.026	23.23 ± 0.511
4	0.93 ± 0.012	23.31 ± 0.347 [90.12%]	0.65 ± 0.009	20.54 ± 0.763
7	0.95 ± 0.012	22.35 ± 0.575	0.54 ± 0.010	18.55 ± 0.259
8	0.93 ± 0.011	21.85 ± 0.436	0.47 ± 0.008	17.53 ± 0.114
9	0.90 ± 0.010	20.48 ± 0.254	0.41 ± 0.011	16.50 ± 0.223
10	0.89 ± 0.011	20.85 ± 0.295	0.39 ± 0.012	16.71 ± 0.370
11	0.88 ± 0.010	19.95 ± 0.205	0.37 ± 0.007	15.96 ± 0.351
14	0.86 ± 0.008	18.64 ± 0.704	0.27 ± 0.009	14.18 ± 0.271
% remaining§	87.20	72.02	30.52	55.25
Equation	y=-0.9385x+100.76	y=-2.055x+100.18	$y=105.51e^{(-0.0862x)}$	$y=998.78e^{(-0.0433x)}$
Time to reach 90% of initial (days)¶	10.74	4.87	1.84	2.13
r^2 value	0.9098	0.9808	0.9927	0.9832

* 1 mg/mL represents the nominal concentration of meropenem.
† 22 mg/mL represents the nominal concentration of meropenem.
§ % remaining on Day 14 relative to Day 0 concentration, expressed as a % of initial concentration.
¶ Time to reach 90% of initial concentration determined through use of the specified equation, determined by least-squared regression of the mean concentration.

mg/mL of meropenem remained clear and colourless throughout the 36-hour period. However, samples containing 22 mg/mL of meropenem changed from a colourless solution to a very light yellow colour over the 36-hour study period.

DISCUSSION

At least 3 factors appear to affect the stability of meropenem. These factors are temperature, concentration and solution or diluent. The effect of temperature is both dramatic and expected, while the effect of diluent was not. However, although dextrose containing solutions do not always have shorter periods of expiration, an increased rate of degradation in dextrose-containing solutions has been reported for ampicillin[7], oxacillin[8], ceftriaxone[9], imipenem[10,11] and vancomycin.[12] Often, this is presumed to be due to pH differences[12], yet the increased rate of degradation is often maintained when there are no differences in pH[7–11]. The situation may be further complicated when both increasing dextrose concentration and increasing hydrogen ion concentration are known to increase the rate of degradation, as is the case for ampicillin[13]. In this study the presence of dextrose increased the rate of degradation. This increase in degradation rate was independent of pH. The effect of dextrose is apparent not only when evaluating differences between NS and D5W, but also explains, in part, the difference in degradation rate for different concentrations of meropenem in D5W. The addition of 50 mg of meropenem to a minibag containing 50 mL of D5W results in 1 mL of sterile water being added to the minibag. This does not change the dextrose concentration to any great extent. However, the addition of 2000 mg of meropenem to a minibag containing 50 mL of D5W results in 40 mL of sterile water being added. This effectively reduces the

Table IV — Summary of meropenem stability in sodium chloride 0.9% in water (NS) and dextrose 5% in water (D5W) with potassium chloride at room temperature.

Nominal meropenem concentration (mg/mL)*	KCl mmol/L (and diluent)†	Time to reach 90% of initial (hours)§	Degradation order	r^2 value
1 D5W	none	4.52	first	0.9985
1 D5W	10 (D5W)	3.33	first	0.9902
1 D5W	40 (D5W)	3.31	first	0.9278
1 D5W	10 (NS)	4.93	first	0.9856
1 D5W	40 (NS)	5.41	first	0.9702
1 NS	none	22.32	zero	0.9804
1 NS	10 (D5W)	5.82	first	0.9942
1 NS	40 (D5W)	6.14	first	0.9931
1 NS	10 (NS)	21.92	zero	0.9706
1 NS	40 (NS)	22.26	zero	0.9748
22 D5W	none	8.07	first	0.9998
22 D5W	10 (D5W)	7.66	first	0.9800
22 D5W	40 (D5W)	7.66	first	0.9931
22 D5W	10 (NS)	13.13	first	0.9603
22 D5W	40 (NS)	12.96	first	0.9936
22 NS	none	17.40	zero	0.9999
22 NS	10 (D5W)	8.08	first	0.9913
22 NS	40 (D5W)	7.95	first	0.9949
22 NS	10 (NS)	20.35	zero	0.9719
22 NS	40 (NS)	20.38	zero	0.9805

* Numbers represent the nominal concentration of meropenem, either 1 mg/mL or 22 mg/mL.
† Numbers represent the nominal concentration of potassium chloride, either 10mmol/L or 40 mmol/L.
§ Time to reach 90% of initial concentration determined by least-squared linear or log-linear regression of the mean concentration.

Table V — Observed time for meropenem to achieve 95% and 90% remaining at 4°C and 23°C.

Storage temperature (°C)	Observed time for meropenem to achieve 95% and 90% remaining in hours (h) or days (d), and % remaining							
	50 mg diluted in 50 mL bag NS (1 mg/mL)*		2000 mg diluted in 50 mL bag NS (22 mg/mL)*		50 mg diluted in 50mL bag D5W (1 mg/mL)*		2000 mg diluted in 50 mL bag D5W (22 mg/mL)*	
4°								
Patel et al†	48 h	96.8	48 h	94.4	6 h	95.25	8 h	[est. 95]
					18 h	90.2	16 h	91.4
Current study§	4 d	95.08	3 d	96.16	1 d	98.94	1 d	94.65
	10 d	91.17	4 d	90.12	2 d	89.80	2 d	90.96
23°								
Patel et al†	11 h	[est. 95]	6 h	[est. 95]	2 h	[est. 95]	2 h	[est. 95
	24 h	90.8	10 h	92.1	4 h	91.6	3 h	92.6
Current study§	11 h	95.07	8 h	95.40	2 h	95.47	4 h	94.97
	22 h	90.14	17 h	90.23	4 h	91.14	8 h	90.19
-20°								
Current study§	14 d	96.5	2 d	98.6	1 d	97.0	2 d	99.2
			11 d	91.1	2 d	86.2	7 d	90.6

* Nominal concentrations of meropenem. NS = sodium chloride 0.9% in water. D5W = dextrose 5% in water.

† Patel et al[3] estimated the concentration at various times over 48 hours, and the time at which 95% actually remained was not observed in all studies. Therefore, in some cases the time to achieve 95% was estimated by interpolation. These cases are designated as [est. 95]. Actual initial concentrations in this study are 1 and 20 mg/mL.

§ To allow comparison betwen the current study and Patel et al[3], the observed time to achieve either 95% or 90% remaining is shown at each temperature for each solution. Actual initial concentrations in this study are 1 and 26 mg/mL

dextrose concentration from 5% to 3% or less, depending on the degree of PVC minibag overfill. At this reduced dextrose concentration the degradation rate is slower (Table II and III). Similarly, mixtures of dextrose and saline solutions (Table IV, compatibility with KCl solutions) produced intermediate degradation rates and admixtures that had no dextrose (saline only) were observed to be more stable. Therefore, as for ampicillin, the presence of dextrose accelerates the degradation rate of meropenem.

Imipenem shows a similar sensitivity to dextrose. Bigley et al10 studied the stability of imipenem at 4°C and 23°C in a variety of intravenous solutions. After storage for 9 hours at room temperature, 250 mg of imipenem in 100 mL of NS was observed to have 94.1% of the initial concentration remaining, while D5W solutions had 86.9% and 10% dextrose solutions had 84.9% remaining.10 This order is maintained for 250 mg/100 mL solutions stored at 4°C and for 500 mg/100 mL solutions stored at 4°C and 25°C.10 In more concentrated dextrose solutions, Zaccardelli et al11 observed that imipenem (5 mg/mL) lost 5% of the initial concentration after storage for 15 minutes in a 25% dextrose TPN solution and 7% was lost in 15 minutes in a 35% dextrose TPN solution. Therefore, it would appear that the presence of dextrose also accelerates the rate of imipenem degradation.

The sensitivity of both meropenem and imipenem to dextrose makes the comparison of expiry dates between these two drugs difficult because the method of preparation may affect the final percentage of dextrose in solution and there is some effect of concentration on stability for both drugs. Meropenem is reconstituted with sterile water (20 mL/1000 mg vial) whereas imipenem may be reconstituted with the intravenous diluent, such as D5W (10 mL/500 mg vial). If either drug is to be admixed in D5W, meropenem solutions will generally have a lower final dextrose concentration due to dilution with sterile water, while the dextrose concentration in the imipenem solution will remain unchanged at 5%. Nevertheless, at similar concentrations in D5W,

Table VI — Maximum recommended periods of storage. NS = sodium chloride 0.9% in water; D5W = dextrose 5% in water.

Storage temperature (°C)	Maximum recommended storage period			
	50 mg diluted in 50 mL bag NS*	2000 mg diluted in 50 mL bag NS†	50 mg diluted in 50 mL bag D5W*	2000 mg diluted in 50 mL bag D5W†
-20°	14 days§	2 days§	Not recomended¶	Not recommended¶
4°	7 days§	3 days§	1 day**	1 day**
23°	22 hours	17 hours	4 hours	8 hours

* Actual initial concentration (taken from Tables II and III) was approoximately 1 mg/mL.
† Actual initial concentration (taken from Tables II and III) was approximately 26 mg/mL.
§ Expiration periods for NS solutions permit storage at room temperature for 6 hours and so are shorter than those found in Tables II and III.
¶ Since storage of meropenem for 6 hours at room temperature in a D5W solution could result in more than 10% loss, it is recommended that, if meropenem must be diluted in D5W, these solutions be used immediately. However, the time constraints related to freezing and thawing a solution, and delivering it to a patient, make freezing of these solutions impractical and not recommended.
** Since storage of meropenem for 6 hours at room temperature in a D5W solution could result in more than 10% loss, it is recommended that, if meropenem must be diluted in D5W, these solutions be used immediately or stored for less than 2 hours at room temperature in addition to 24 hours storage at 4°C.

imipenem and meropenem have similar stabilities. Solutions of imipenem 2.5 mg/mL in D5W stored at 23°C, have been reported to have 90.4% remaining after 4 hours10 compared to 91.6 % remaining after 4 hours[3] and 91.1% reported after 4 hours in this study for 1 mg/mL meropenem solutions in D5W. Similarly, when comparing high doses, 5 mg/mL solutions of imipenem in D5W stored at 23°C have been reported to have 93.8% remaining after 3 hours[10] and 90.6 % remaining after 6 hours.[14] In comparison, 22 mg/mL of meropenem in D5W stored at 23°C was observed to have 92.6% remaining after 3 hours[3] and in this study we observed 90.2 % remaining after 8 hours. The degradation rate is also roughly equivalent in saline solutions. At 4°C, Bigley et al[10] reported that a 5 mg/mL imipenem solution retained 92.7% after 72 hours, whereas, in this study, a 22 mg/mL solution of meropenem retained more than 90% of the initial concentration for 4 days (rate of loss of approximately 2.5% per day for both solutions).

Stability information previously available on meropenem indicated that vials which are freshly reconstituted with sterile water are stable for 2 hours at room temperature and up to 12 hours at 4°C.[2] Once reconstituted, solutions that are further diluted in normal saline are stable for 4 hours at room temperature and 24 hours at 4°C. When meropenem is diluted in D5W, solutions are considered stable for 1 hour at room temperature and 4 hours at 4°C. The results generated by Patel et al[3] report expiry dates which are much longer than those which appear in the prescribing information2 and the difference is due to the fact that expiry dates in the prescribing information are determined based on the time to achieve a concentration of 95%. However, when these 2 reports and the current study are compared there is reasonable agreement after giving consideration to differences in concentration. Nevertheless, the current study reports a slower rate of loss at 4°C than does Patel et al[3] (Table V). The reason for this is not entirely obvious since the chromatographic method is virtually identical and care was taken in the current study to reduce degradation following sample preparation prior to chromatography.

Patel et al[15] reported Y-site compatibility of 1 mg/mL and 50 mg/mL of meropenem in saline with a variety of medications and found most agents except diazepam, calcium gluconate, ondansetron, zidovudine and calcium gluconate to be compatible. Potassium chloride was not reported. This study has demonstrated that meropenem is compatible with potassium chloride and that potassium chloride does not affect the stability of meropenem at room temperature.

RECOMMENDED SHELF-LIVES FOR MEROPENEM

Meropenem solutions, as for all intravenous medications, will generally be brought to room temperature prior to being given to a patient. Therefore, any recommended shelf-lives must allow for storage at room temperature. For intravenous solutions of meropenem which are never frozen, the shelf-lives found in Table VI are recommended. These recommendations are based on calculations which combine degradation rates observed at room temperature (23°C) and in the refrigerator (4°C) in this study. Therefore, a solution of meropenem of 50 mg diluted in a 50 mL bag of NS (1 mL of meropenem solution following reconstitution of 1000 mg of Merrem® with 20 mL of sterile water is added to a minibag containing 50 mL of NS yielding a nominal concentration of 50 mg/~50 mL) could be stored at 4°C for 7 days. This storage period would allow for up to an additional period of 6 hours storage at room temperature. However, for D5W solutions, because 10% of the initial concentration will be lost on storage at room temperature within 8 hours, depending on the concentration, we recommend that D5W solutions be freshly prepared and administered immediately. Preparation of meropenem solutions in D5W may place unreasonable constrictions on an IV additive program and lead to substantial drug wastage[1]. Therefore, to reduce wastage we recommend that meropenem solutions be diluted in saline solutions and stored at 4°C for up to 7 days.

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