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Environmental and Matrix-Dependent Stability of Meropenem: A Comparative Study in Solvents and Human Plasma

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currently employed by CoQua Lab srl. Antonio D'Avolio reports a relationship with CoQua Lab srl that includes: equity or stocks. The authors declare that they have no known competing financial interests or personal re-lationships that could have appeared to influence the work reported in this paper.

Abstract

Meropenem (MEM) is a β-lactam carbapenem antibiotic whose efficacy depends on maintaining drug concentrations above the minimum inhibitory concentration (MIC). Due to high variability in pharmacokinetics among patients, therapeutic drug monitoring (TDM) is essential for optimizing dosing. However, MEM is chemically unstable and its stability is affected by solvent type and storage conditions. While previous studies have examined MEM stability in aqueous solutions, limited information exists on its behaviour in organic solvents and in plasma matrices, which are critical for accurate sample handling and analysis.

Stability studies were conducted by dissolving MEM in water and DMSO and subjected to four freeze–thaw cycles at -80°C and − 20°C. Additionally, MEM concentrations were measured after 1 and 3 hours at room temperature. Parallel stability studies were conducted with MEM spiked into blank plasma samples under the same conditions.

This study highlights the critical impact of solvent choice and sample handling on the chemical stability of MEM, helping all those who will use the drug in studies and/or analyses.

Introduction

Meropenem (MEM) is a β-lactam antibiotic belonging to the class of carbapenems. It is commonly utilized in clinical practices for the treatment of a wide range of bacterial infections (both Gram-positive and Gram-negative)[1–3]. MEM exhibits time-dependent antibacterial activity; thus, its bactericidal efficacy is strongly associated with the duration for which drug concentrations exceed the minimum inhibitory concentration (MIC)[4]. The parameter T > MIC is a critical determinant of therapeutic effectiveness. Conversely, when concentrations fall below the MIC (T < MIC), bacterial regrowth occurs promptly, as MEM lacks a significant post-antibiotic effect [5, 6]. To maximize its time-dependent bactericidal activity, MEM is administered via continuous-infusions [5, 7, 8]. However, MEM pharmacokinetics demonstrated to be significantly variable among patients, possibly invalidating the therapeutic outcomes of the therapy [9]. In this scenario, therapeutic drug monitoring (TDM) represent a useful strategy to guide individualized dosing and improve clinical efficacy [10, 11]. However, accurate MEM quantification within the TDM framework depends critically on its stability under conditions that reflect routine sample handling and preparation.

Chemically, MEM is a white crystalline compound characterized by pKa values of approximately 2.9 and 7.4. MEM chemical structure is represented in Fig. 1. It demonstrates poor aqueous solubility and is prone to hydrolytic degradation owing to its β-lactam ring structure [6, 7]. The stability of reconstituted MEM solutions is known to be influenced by both storage temperature and the type of solvent used for reconstitution. Indeed, several studies demonstrated that carbapenems, including MEM, are relatively unstable in particular solution conditions [5, 9, 10, 12–14]. As an example, Jamieson et al. (2020) conducted a study to investigate the stability of MEM in various buffer solutions with different pH values. They found that even under optimal storage conditions (pH around 7 and a MEM concentration of 6.25

mg/mL), there was a 10% loss of the analyte after 24 hours of storage at 32°C [10]. Similarly, in a 2019 study by Fawaz et al., the authors demonstrated that at 33°C in aqueous solutions, 90% of MEM was maintained only for the first 5.7 hours, while, after 20 hours, just 61.4% of the initial concentration of MEM remained [5].

Although these investigations offer important information, limited research has been conducted on the stability of MEM in organic solvents. Moreover, the possible stabilizing role of plasma matrices following MEM spiking, along with the effects of storage conditions pertinent to sample handling and processing, remains insufficiently explored [9].

In light of the current knowledge gaps, the present study aimed to evaluate the stability of MEM in dimethyl sulfoxide (DMSO) and water, both before and after spiking into blank plasma samples. MEM degradation at room temperature was assessed under each of the aforementioned conditions.

To enable precise and reliable quantification, MEM concentrations were determined using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method.

Matherial and methods

Chemicals and reagents

The MEM reference standards (purity > 98%) were supplied by Shimadzu Chemistry & Diagnostics (France). DMSO was purchased by Sigma-Aldrich (St. Louis, Missouri, Stati Uniti). HPLC grade water was obtained by Carlo Erba Reagents srl (Milan).

Stock solutions and plasma samples preparations

Stock solutions were prepared by dissolving the pure drug powder according to the specifications provided in the certificates of analysis. The solution was then added to human blank plasma to obtain plasma sample at a concentration of 1000 ng/ml. Human blank plasma was obtained from the Blood Component Production and Validation Centre at Molinette Hospital, Turin, Italy

LC-MS/MS Analysis

Stability assessments of MEM were performed using the validated LC-MS/MS kit by CoQua lab (Turin, Italy) [15]. The chromatographic analysis was carried out on the Acquity UPLC H-Class Plus system coupled with a Xevo TQ-S micro detector.

Stability studies

MEM standard was dissolved in two different solvents, HPLC grade water and DMSO, at a concentration of 10 µg/ml. To assess the stability of MEM in the two different dissolution solvents, four freeze–thaw cycles were performed under two different storage conditions, -80°C and – 20°C. In addition, the changes of MEM concentration at room temperature were also evaluated after 1 hour and 3 hours.

To evaluate the stability of MEM in plasma, four freeze–thaw cycles were conducted under two separate storage conditions (-80°C and – 20°C). Furthermore, variations in MEM concentration at room temperature were monitored after 1 and 3 hours.

Results

1. Short term stability of MEM at room temperature in water and DMSO

Figure 2 illustrates the stability profile of MEM in different solvents at room temperature. When dissolved in water, MEM remained relatively stable over a period of 3 hours, with relative standard deviations (RSD%) of -12.84% at 1 hour and -8.02% at 3 hours. In contrast, MEM in DMSO exhibited a rapid and substantial degradation, with a concentration decrease of over 50% already evident after the first hour (1-hour RDS%: -57%). After 3 hours, only 36% of the initial MEM concentration was detectable in the DMSO samples. The raw data from the following experiment are reported in *Table 1*.

A	**DMSO**	
	Response	**RSD%**
0	88,23	-
1h	37,91	-57%
3h	31,57	-64%

B	**H_2O**	
	Response	**RSD%**
0	69,62	-
1h	60,68	-12,84%
3h	64,03	-8,02%

Table 1 A-B Short-Term stability of meropenem in DMSO (initial concentration: 10 µg/ml). B Short-Term stability of meropenem in water (initial concentration: 10 µg/ml). Stability was evaluated based on the analyte response, defined as the peak area of meropenem normalized to the internal standard peak area.

2. Freeze and thaw stability of MEM in DMSO

The stability of MEM in DMSO following four freeze-thaw cycles was comparable at both -80 °C and -20 °C. As shown in *Figure 3*, more than 30% of the initial MEM concentration was lost after the first cycle (RSD%: -33% at -80 °C and -43% at -20 °C). Subsequent cycles led to a progressive reduction in concentration, with approximately 80% of the initial MEM degraded by the fourth cycle (RSD%: -80% at -80 °C and 77% at -20 °C). Raw data reported in *Table 2*.

	80 °C		20 °C	
	Response	**RSD%**	**Response**	**RSD%**
Fresh sample	**54,7**	**-**	**54,7**	**-**
1°cycle	**36,7755**	**-33%**	**31,08**	**-43%**
2°cycle	**20,4715**	**-63%**	**22,287**	**-59%**
3°cycle	**12,146**	**-78%**	**11,406**	**-79%**
4°cycle	**10,7695**	**-80%**	**12,44**	**-77%**

Table 2 Freeze-thaw stability of Meropenem in DMSO at −80 °C and −20 °C (initial concentration 10 µg/ml). Stability was evaluated based on the analyte response, calculated as the peak area of meropenem normalized to the internal standard peak area.

3. Freeze and thaw stability of MEM in plasma

Freeze-thaw stability of MEM in plasma was evaluated at both -80 °C and -20 °C. Plasma samples were prepared using an initial dilution in DMSO. As illustrated in *Figure 4*, the presence of plasma significantly altered the behaviour of MEM during freeze-thaw cycles. Notably, after the first freeze-thaw cycle, an increase of approximately 30% in the measured MEM concentration was observed at both temperatures (RSD% after first cycle at -80 °C: 29%; at -20 °C: 25%).

In contrast, subsequent freeze-thaw cycles did not lead to further changes in the detected concentration. The RSD% remained stable and did not exceed 30% even after four cycles (RSD% after first cycle at -80 °C: 24%; at -20 °C: 24%). Raw data reported in *Table 3*

	80°C		20°C	
	Response	**RSD%**	**Response**	**RSD%**
Fresh sample	0,879	-	0,879	-
1°cycle	1,13	29%	1,1015	25%
2°cycle	1,011	15%	1,094	24%
3°cycle	1,1305	29%	1,0415	18%
4°cycle	1,092	24%	1,089	24%

Table 3. Freeze-thaw stability of Meropenem in plasma at -80 0 °C and −20 °C (initial concentration 10 µg/ml). Stability was evaluated based on the analyte response, calculated as the peak area of meropenem normalized to the internal standard peak area.

4. Short term stability of MEM in plasma

MEM stability in plasma was evaluated in two experimental conditions. In the first experiment (*Figure 5A*) plasma samples were spiked with MEM, previously pre-diluted in water (orange line in the graph) or DMSO (blue line in the graph), at time 0, and analysed after 1 and 3 hours of storage at room temperature. The results indicate a slightly greater degradation of MEM when prediluted in DMSO, with a relative signal decrease of 9% after 1 hour (RSD% 1-hour DMSO: -9%) compared to a 3% decrease observed with the water pre-dilution (RSD% 1 hour water: - 3 %). However, in both conditions, the presence of plasma appears to mitigate MEM degradation over time. Indeed, no substantial variation was observed between 1 and 3 hours, with RSD% values of -11% in DMSO and - 2 % in water respectively. Raw data reported in *Table 4*

In the second experiment, MEM predilutions were prepared at time 0 and stored at room temperature for 1 and 3 hours. Plasma samples were then spiked immediately before the analysis. Unlike from the first experiment, a marked difference was observed between pre-dilution in DMSO and water (*Figure 5B*). Consistent with the findings shown in *Figure 2*, MEM degradation occurred more rapidly in DMSO, with a 64% decrease in concentration after 3 hours, compared to only an 8% decrease in water. In this setting, the presence of plasma did not attenuate the degradation process, which had already occurred during the pre-dilution phase, prior spiking. Raw data reported in *Table 4*

A	**Predilution in DMSO**		**Predilution in H2O**	
	Response	RSD%	Response	RSD%
0	1,6185	-	1,4145	-
1h	1,47	-9%	1,366	-3%
3h	1,442	-11%	1,3845	-2%

B	Predilution in DMSO		Predilution in H2O	
	Response	RSD%	Response	RSD%
0	1,6185	-	1,4145	-
1h	1,1645	-28%	1,409	0%
3h	0,6615	-59%	1,599	13%

Table 4 A-B Short-Term stability of meropenem (initial concentration: 10 µg/ml). A: Plasma samples were spiked with MEM pre-diluted in water or DMSO at time 0, then stored at room temperature for 1 and 3 hours before the analysis. B MEM predilutions in water and DMSO were prepared at time 0 and stored at room temperature for 1 and 3 hours, plasma samples were spiked immediately before the analysis. Stability was evaluated based on the analyte response, defined as the peak area of meropenem normalized to the internal standard peak area.

Discussion and conclusion

This study provides a detailed characterization of the chemical stability of the compound MEM under various experimental conditions, with a focus on solvent effects, freeze-thaw cycles, and the protective role of plasma. In particular, the results show the critical influence of MEM standard handling protocol, which has direct implications for both experimental reproducibility and the reliability of bioanalytical measurements.

According to previous results found in literature, MEM demonstrated distinct stability profiles depending on the solvent used[16, 17]. When reconstituted in water, MEM exhibited relatively minor degradation over short-term exposure at room temperature, with only modest reductions analyte concentration observed after three hours *(Figure 2*). In contrast, MEM dissolved in DMSO underwent rapid degradation, with over 50% loss occurring within the first hour (*Figure 2*). The observed rapid degradation indicates that, although DMSO is commonly employed as a solvent for compounds with low aqueous solubility, it may facilitate the degradation pathways, possibly due to its physicochemical properties or interactions with the β-lactam ring)[18, 19]. These data are in accordance with previous results found in literature which demonstrated the susceptibility of carbapenems to hydrolytic degradation under specific solvent conditions [2, 5].

Freeze -thaw stability experiment further supported the instability of MEM in DMSO. Substantial degradation was observed after the initial cycle, with progressive deterioration across subsequent cycles, with no differences observed between storage at -20 °C or -80 °C (*Figure 3*). The loss of over 75% of the initial concentration by the fourth cycle underscores the unsuitability of DMSO as a storage medium for repeated freeze-thaw conditions.

Interestingly, plasma appeared to exert stabilizing effects on MEM degradation. An increase of approximately 30% in MEM signal intensity after the first freeze-thaw cycle in plasma sample suggests a matrix effect that may either protect the compound or influence analyte recovery during analysis. Importantly, no significant degradation occurred in subsequent cycles, further supporting the protective role of plasma (*Figure 4*). Similarly, in short term stability experiments, plasma demonstrated a mitigating effect of MEM degradation. Indeed, a marked difference in MEM concentration was observed in the two experimental conditions studied. Moreover, the timing of plasma addition also emerged as a key determinant of compound stability. When MEM was spiked into plasma immediately after pre-dilution in either water or DMSO, only a minor degradation was observed after three ours. On the other hand, when prediluted solutions were stored prior to plasma spiking, the degradation profile resembled that of solvent alone, with rapid loss in DMSO and a more modest decline in water (*Figure 5***).** This distinction highlights the importance of timing in sample preparation and suggest that early exposure to stabilizing matrices such as plasma can significantly reduce MEM degradation.

Taken together, these results demonstrate that both solvent choice and handling protocol critically impact MEM stability. For accurate quantification and reliable pharmacokinetic monitoring, MEM should preferably be handles in aqueous solvents, with minimal delay between dilution and plasma spiking. DMSO should be avoided in MEM sample preparation as well as repeated freeze and thaw cycles during sample storage. Furthermore, the demonstrated stability in plasma supports the feasibility of TDM methodologies relying on plasma-based bioanalytical workflows, provided that appropriate pre-analytical precautions are observed [20].

Future research should aim to elucidate the specific chemical pathways underlying MEM degradation in DMSO and other solvent systems. Additionally, further exploration of protein-binding interactions in plasma may elucidate the mechanisms behind the observed stabilization effect. Collectively, this study provides a preliminary framework for understanding the stability profile of MEM and offers methodological recommendations for its use in both in vitro applications and pharmacokinetic studies.

Abbreviations

Meropenem (MEM); minimum inhibitory concentration (MIC)¸ therapeutic drug monitoring (TDM)¸ Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS); Relative Standard Deviation (RSD).

Declarations

Ethics approval

This study did not require ethics committee approval or institutional review board (IRB) oversight, as it did not involve human participants, human data, or human tissue. The experiments were conducted exclusively using commercially available blank plasma matrix for the purpose of analyte stability testing, with no involvement of identifiable human subjects.

Accordance Statement

As no human participants, human-derived data, or human tissue were involved in this study, the requirements of the Declaration of Helsinki are not applicable. All laboratory procedures were carried out in accordance with relevant institutional guidelines, Italian national regulations governing research ethics (Italian Legislative Decree No. 211/2003 and Legislative Decree No. 52/2019), and standard Good Laboratory Practice (GLP) principles as defined by Italian Legislative Decree No. 50/2002, which implements OECD GLP guidelines in Italy.

Consent to Participate

Informed consent to participate was not required, as this study did not involve human participants, patient data, or biological samples obtained from identifiable individuals. In accordance with Italian national regulations — specifically Italian Legislative Decree No. 211/2003 and Legislative Decree No. 52/2019 — ethics review and informed consent obligations apply exclusively to clinical trials and studies involving human subjects. The exclusive use of commercially sourced blank plasma for analytical method validation purposes falls outside the scope of these regulatory requirements.

Consent for publication

Not applicable

Availability of data and materials

Data are available on request by the corresponding author.

Competing Interests

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. Giorgia Menegatti, Fabio Favata, Elena Cat Genova and Domenico Maiese are currently employed by CoQua Lab srl. Antonio D'Avolio reports a relationship with CoQua Lab srl that includes: equity or stocks. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Conceptualization, A.D. and F.F.; methodology, M.B.; software, G.M.; validation, M.B., G.M. and E.C.G.; formal analysis, M.B and C.M..; investigation, G.M.; resources, D.M and E.C.G.; data curation, G.M and

F.F.; writing—original draft preparation, M.B and G.M.; writing—review and editing, A.D.; visualization, F.F.; supervision, A.D.; project administration, F.F.; funding acquisition, A.D. All authors have read and agreed to the published version of the manuscript.

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Figures

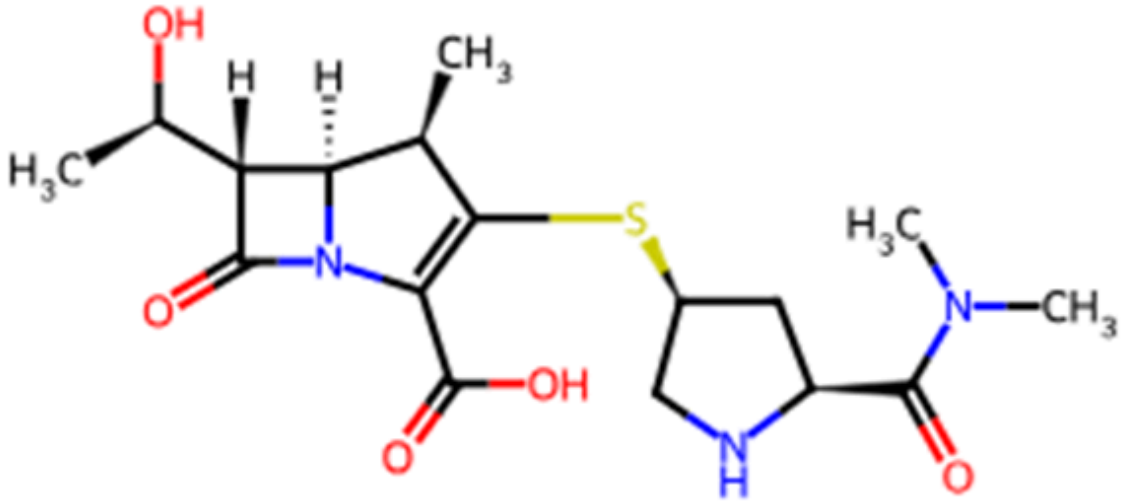


Figure 1

Meropenem chemical structure

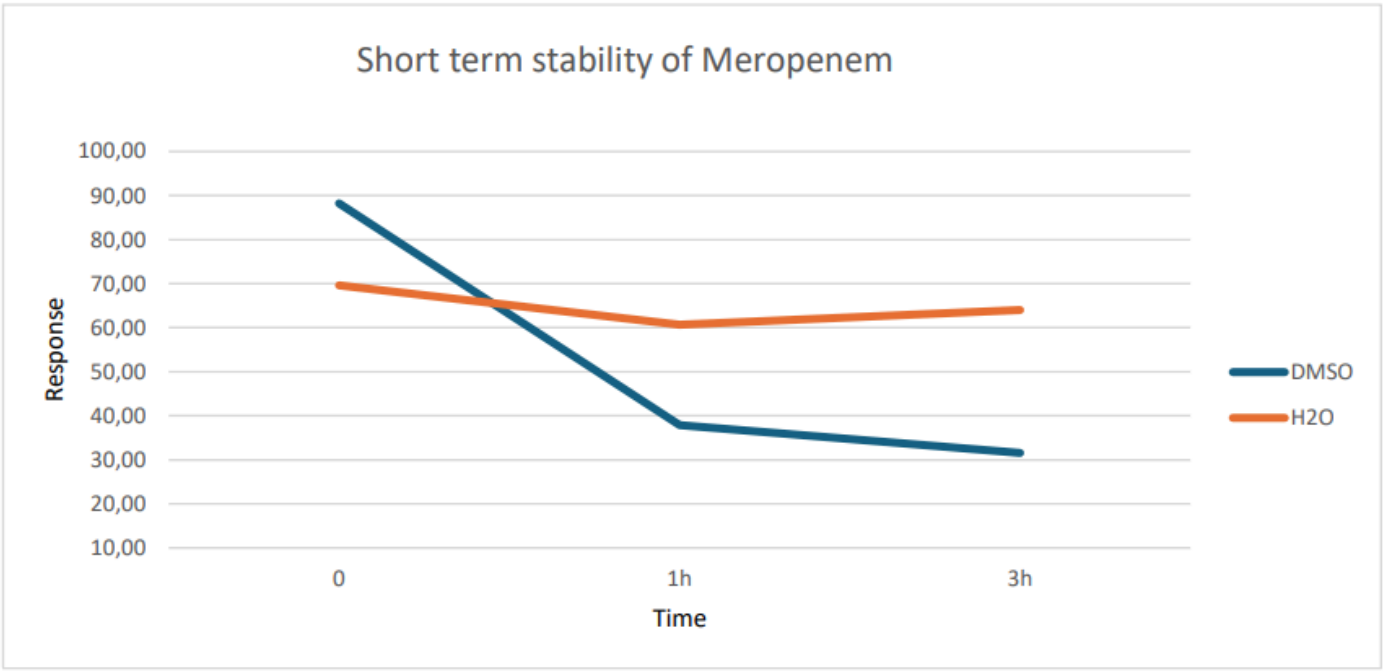


Figure 2

Short-Term stability of meropenem (initial concentration: 10 µg/ml). Stability was evaluated based on the analyte response, defined as the peak area of meropenem normalized to the internal standard peak area. The orange line represents meropenem stability in water, while the blue line indicates its stability in DMSO.

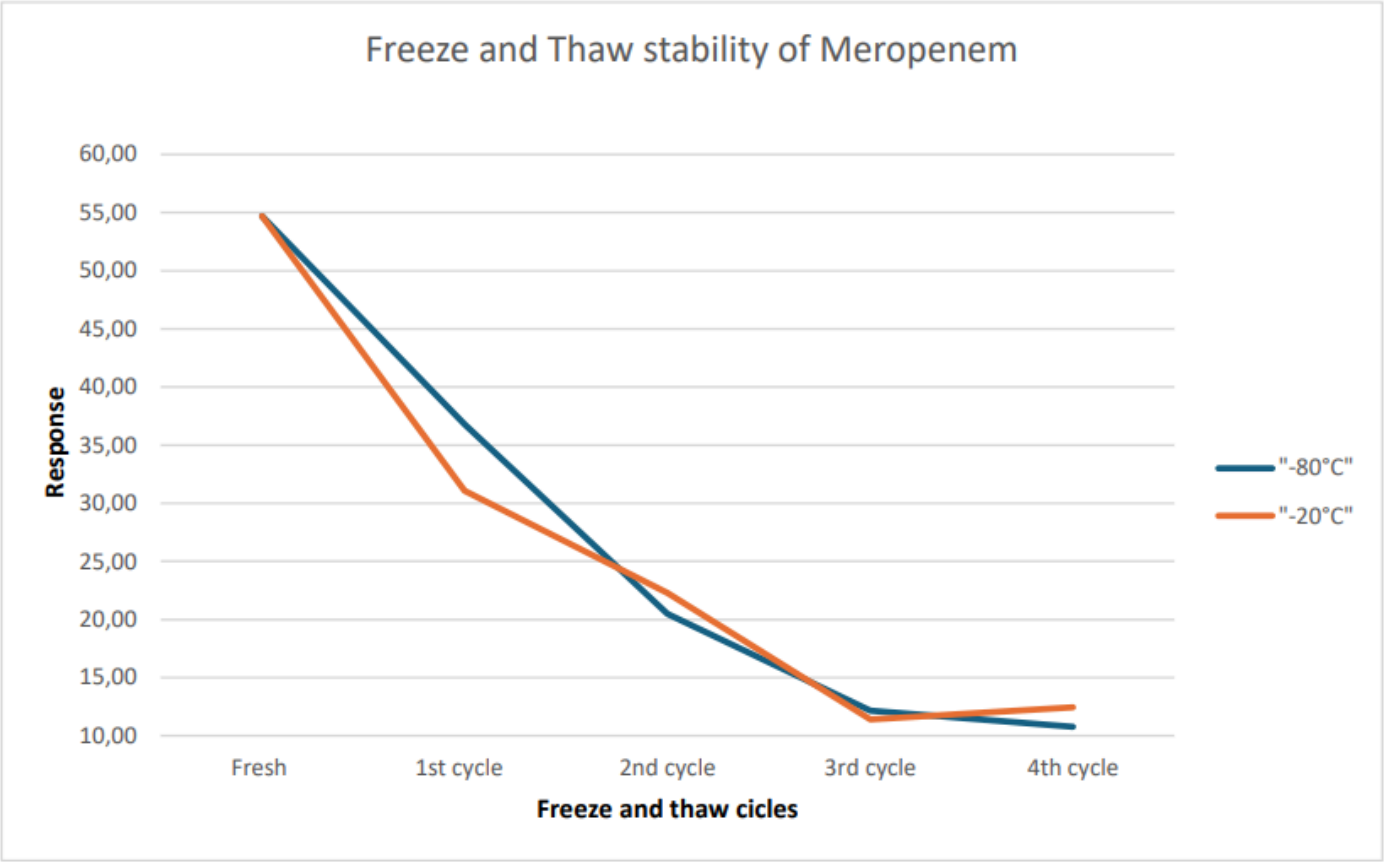


Figure 3

Freeze-thaw stability of Meropenem in DMSO at −80 °C and −20 °C (initial concentration 10 µg/ml). Stability was evaluated based on the analyte response, calculated as the peak area of meropenem normalized to the internal standard peak area. The orange line represents samples stored at −20 °C, while the blue line corresponds to those stored at −80 °C.

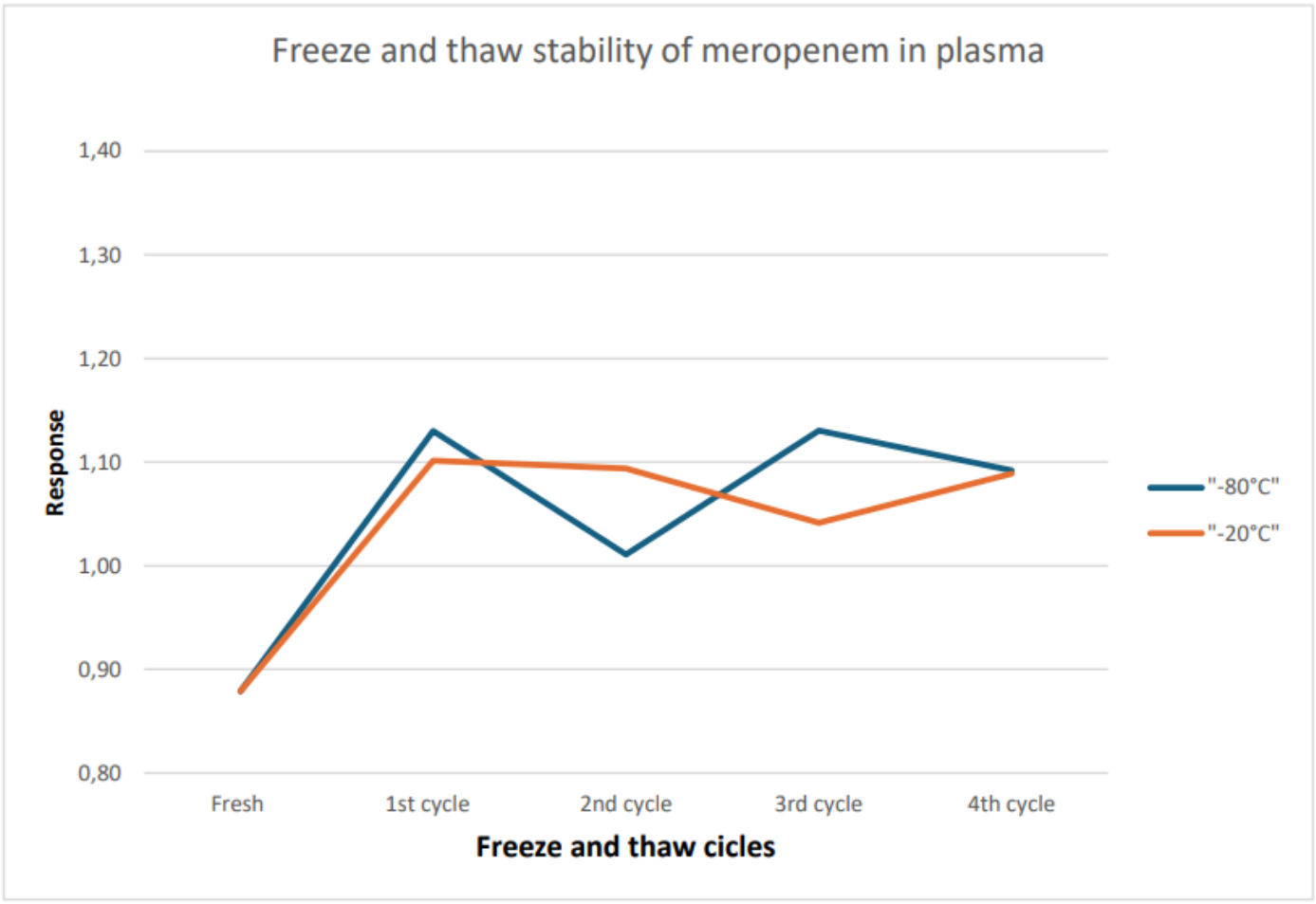


Figure 4

Freeze-thaw stability of Meropenem in plasma at -80 0 °C and −20 °C (initial concentration 10 µg/ml). Stability was evaluated based on the analyte response, calculated as the peak area of meropenem normalized to the internal standard peak area. The orange line represents samples stored at −20 °C, while the blue line corresponds to those stored at −80 °C.

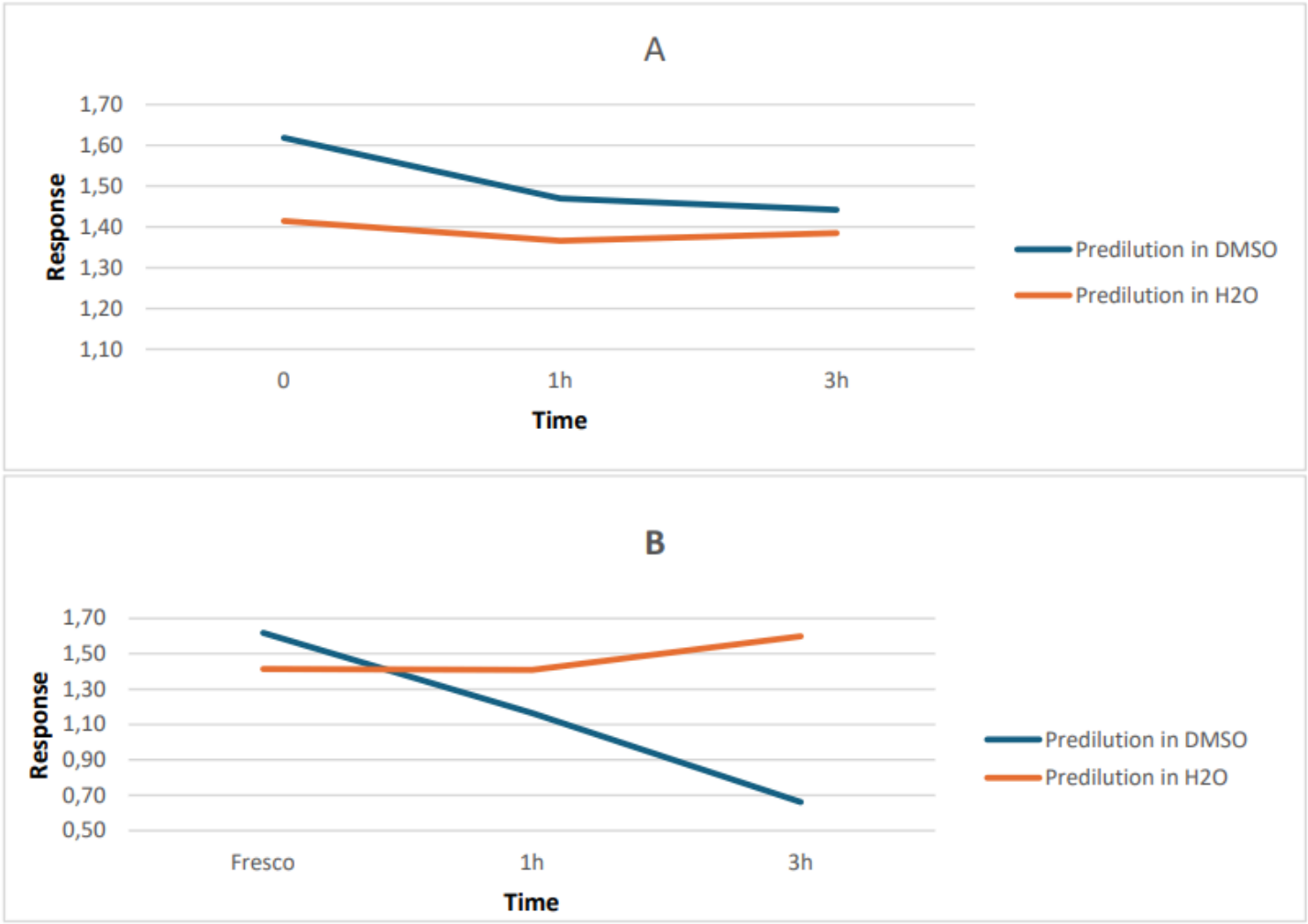


Figure 5

A-B Short-Term stability of meropenem (initial concentration: 10 µg/ml). A: Plasma samples were spiked with MEM pre-diluted in water (orange line) or DMSO (blue line) at time 0, then stored at room temperature for 1 and 3 hours before the analysis. B MEM predilutions in water (orange line) and DMSO (blur line) were prepared at time 0 and stored at room temperature for 1 and 3 hours, plasma samples were spiked immediately before the analysis. Stability was evaluated based on the analyte response, defined as the peak area of meropenem normalized to the internal standard peak area.