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An ultra-high-performance chromatography method to study the long term stability of gemcitabine in dose banding conditions

Mélanie Closset [a,d,*], Marie-Lise Colsoul [a,d], Nicolas Goderniaux [a,d], Benoît Bihin [c,d], Jacques Jamart [d], Sabrina Onorati [a], Laura Soumoy [b,d], Jean-Daniel Hecq [d], Pascal Odou [e], Laurence Galanti [a,d]

[a] Medical Laboratory, CHU UCL Namur, 1 Avenue Therasse, 5530 Yvoir, Belgium
[b] Department of Pharmacy, CHU UCL Namur, 1 Avenue Therasse, 5530 Yvoir, Belgium
[c] Scientific Support Unit, CHU UCL Namur, 1 Avenue Therasse, 5530 Yvoir, Belgium
[d] Drug Stability Research Group, CHU UCL Namur, 1 Avenue Therasse, 5530 Yvoir, Belgium
[e] Université de Lille, CHU Lille, ULR7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, F-59000 Lille, France

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ABSTRACT

Gemcitabine is an analogue of cytidine arabinoside, used alone or in combination chemotherapy to treat various type of cancer. The dose-banding of gemcitabine provides the opportunity to anticipate the preparation of this anticancer drug on condition of carrying out stability studies. The aim of this study is to develop and validate a stability-indicating ultra-high-performance Liquid Chromatography (UHPLC) method for measuring the concentration of gemcitabine and to evaluate its stability at standardised rounded doses in polyolefin bags. The UHPLC with photodiode array (PDA) detector method was developed and validated (linearity, precision, accuracy, limits of detection and quantification, robustness and degradation test). Thirty polyolefin bags of gemcitabine (1600 mg/292 ml (n = 10), 1800 mg/297 ml (n = 10) and 2000 mg/303 ml (n = 10)) were prepared under aseptic conditions and stored at 5 ± 3 °C and 23 ± 2 °C for 49 days. Physical stability tests were periodically performed: visual and microscopic inspection and optical densities. The chemical stability was evaluated through pH monitoring and chromatographic assays. The results confirm the stability of Gemcitabine at selected standardised rounded doses of 1600 mg, 1800 mg and 2000 mg in NaCl 0.9% polyolefin bags for at least 49 days at 5 ± 3 °C and 23 ± 2 °C, allowing in-advance preparation.

1. Introduction

Gemcitabine, an analogue of cytidine arabinoside with broad-spectrum activity [1], is used as a single agent as well as in combination chemotherapy in various indications including pancreatic [2], non-small cell lung, bladder [3], breast, ovarian, head and neck cancers and mesothelioma [4].

Liquid chromatographic methods with UV detector [5–9] have usually been described to measure the gemcitabine concentration as well as more recently chromatographic methods coupled to mass spectrometry [10–13] more sensitive but also more expensive and complicated.

The drug dosing of the gemcitabine is a key issue as for other cytotoxic molecules. Dose-banding appears as an alternative to body surface area dosing of anticancer drug [14–17] where the doses – still calculated on an individualised base – are rounded up or down to predetermined standard doses (standard rounded doses or SRD) with a maximum variation of the adjustment of 5% or less [18]. This allows to prepare anticancer drug in advance in a secure production environment by a centralised pharmacy service [19–21] and then to improve safety for the patients and to reduce their waiting time in day care units [22–24]. The gemcitabine stability in these conditions must therefore be known.

Stability studies have been carried out for specific concentrations and containers. Ponton et al. [8] focused on gemcitabine (7.5 and 25 mg/ml) in glass bottles and polyvinyl chloride (PVC) infusion bags at 25 °C while Xu et al. [9] studied the molecule stability at 0.1, 10 and 38 mg/ml in original vials, plastic syringes and PVC minibags at 4 and 23 °C for 35 days and 32 °C for 7 days. However, none of them studied gemcitabine under the dose-banding conditions of 1600, 1800 and 2000 mg in polyolefin bags classically used in clinics [25].

In this study, a simple, accurate and stability-indicating ultra-high

* Corresponding author at: Medical Laboratory, CHU UCL Namur, 1 Avenue Therasse, 5530 Yvoir, Belgium.
E-mail address: melanie.closset@chuuclnamur.uclouvain.be (M. Closset).

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pressure liquid chromatography (UHPLC) method coupled with a PDA detector was developed to evaluate the gemcitabine stability in dose banding conditions.

2. Aim of the study

The aim of this study is to develop and validate an UHPLC method for measuring the concentration of gemcitabine and to evaluate its stability at standardised rounded doses in polyolefin bags at 5 ± 3 °C and 23 ± 2 °C.

3. Materials and methods

3.1. Solutions preparation

Thirty bags of gemcitabine were prepared under aseptic conditions and stored for 49 days. The bags were composed of gemcitabine (38 mg/ml, FRESENIUS KABI, lot 87210090BA) and 0.9% sodium chloride solution (MACOPHARMA, lot 20I15B) to prepare the banding doses of 1600, 1800 and 2000 mg. The composition of the bags is listed in Table 1.

3.2. Chromatographic assay

Gemcitabine was measured with an ultra-high-performance liquid chromatography (UHPLC; Acquity UPLC H-Class, Waters, Milford, USA) system coupled to a photodiode array detector (PDA; Acquity, Waters) set at 275 nm and to a processing module (Empower 3 Software, Waters Association, Milford, MA, USA). The column was a reversed-phase C18 (Luna® Omega, 1.6 µm, 100 Å, 100 ×2.1 mm, Phenomenex, H16–360891) kept at 30 °C with an isocratic mobile phase composed of 95% phosphate buffer (Na2HPO4 / KH2PO4, pH7) 0.01 M and 5% acetonitrile at a flow rate of 0.4 ml/min.

3.3. Validation of the UHPLC method

The chromatographic method was validated following the international conference on harmonisation (ICH) guidelines Q2(R1) [26] with the evaluation of several parameters as precision, accuracy, linearity, limit of detection, limit of quantification, robustness and stability-indicating capability of the method.

The intra (n = 10) and inter-assay (n = 10) precisions were assessed using the three quality control solutions (C1 = 3 mg/ml, C2 = 5 mg/ml and C3 = 7 mg/ml). Precision was determined in terms of percentage relative standard deviation (RSD%).

To verify the agreement between a “true" value and the value found, the accuracy was calculated based on the reference values of the quality controls solutions compared to the found values as follows:

$$\text{Bias}(\%) = \frac{measuredvalue - expectedvalue}{expectedvalue} * 100$$

The linearity was evaluated by two-fold serial dilutions (n = 10) in purified water from a gemcitabine solution of 15 mg/ml.

The limits of detection (LOD) and quantification (LOQ) were calculated based on a blank. Purified water was injected 10 times and the background noise at the gemcitabine retention time was quantified. The mean and standard deviation were determined on this basis and LOD and LOQ calculated as follows.

$$\text{LOD} = \text{mean} + 3 \text{ x standard deviation}$$

$$LOQ = mean + 10\ x\ standard\ deviation$$

The robustness of the method was evaluated through a deliberate variation in the pH of the mobile phase. Several pH between 6.5 and 7 were tested and the RSD % obtained for the controls (C1, C2, C3) were compared to those of the interassay precision. Variation in other parameters such as temperature or flow rate were not challenged given that they were under control of the system (absence of human intervention).

The stability-indicating capability of the method was assessed through a forced degradation of samples. Vials containing 1 ml of a fresh solution of gemcitabine (6.65 mg/ml) were prepared in neutral, acidic (HCl 0.2 M), alkaline (NaOH 0.2 M) and oxidative (H_2O_2, 3%, Lot STBH5484; Sigma-Aldrich, Overijse, Belgium) conditions. Acidic and alkaline solutions were neutralised before injection. Solutions were injected immediately after preparation and after 2 and 4 days of preservation at room temperature and at 60 °C.

3.4. Stability study

For each prepared band (1600, 1800 and 2000 mg), five bags were stored at 5 ± 3 °C and the five others at 23 ± 2 °C to compare storage conditions.

Aliquots were withdrawn to perform physicochemical stability tests every day the first week, 3 times a week for three weeks and then one time a week for four weeks. The physical tests were straight performed on dedicated aliquots while aliquots dedicated to the chemical tests were frozen (−20 °C)[27].

3.4.1. Physical stability

Samples were visually inspected in front of black and white backgrounds to identify colour changes, haze, precipitation or particles.

A spun aliquot (5 min at 2150 g, Heraeus multifuge 1 S, Thermo Scientific, USA) was observed under a microscope (Jenamed, Carl Zeiss, Germany) with an 80-fold magnification to detect crystal formation.

Optical densities were measured at 350, 410 and 550 nm (Genesys 10 UV, Spectronic Unican) at each time point to check the apparition of turbidity in order to detect the occurrence of subvisible particle [28].

3.4.2. Chemical stability

3.4.2.1. pH. The pH of the solution was monitored with a glass electrode pH-meter (InoLab, WTW GmbH, Weilheim, Germany).

3.4.2.2. Chromatographic assays

3.4.2.2.1. Standard and quality control solutions. Each working day, five levels of standard solutions were prepared using the commercial solution of gemcitabine 38 mg/ml diluted in purified water (2, 3, 5, 7 and 10 mg/ml) to determine the calibration curve.

Three quality control solutions (3, 5 and 7 mg/ml) were prepared following the same procedure.

Standard and quality control solutions were injected in the system after a hundred-fold dilution.

3.4.2.2.2. Samples. Aliquots stored for the chemical study were defrosted by batch just before chromatographic analyses. The chemical analysis was made in triplicate after a hundred-fold dilution.

3.5. Statistical analyses

The statistical analysis of the chemical stability of gemcitabine is

Table 1
Composition of infusion bags of gemcitabine (bands of 1600, 1800 and 2000 mg).

Number of bags	Bands (mg)	Preparation		Final Concentration of gemcitabine (mg/ml)
		Volume of gemcitabine (ml)	Volume of NaCl 0.9% (ml)	
10	1600	42	250	5.47
10	1800	47	250	6.01
10	2000	53	250	6.65

based on a linear mixed model. In this model, the response is the logarithm of the concentration of gemcitabine, the fixed effects are the time (in weeks), the temperature (5 ± 3 °C or 23 ± 2 °C), the doses (1600 mg, 1800 mg or 2000 mg) as well as the interactions between time, temperature and doses. This model also incorporates a random intercept and a random slope per bag to account for correlation between measurement made on the same bag.

Based on this model, the fitted values, the lower limit of the one-sided 95% confidence interval on the mean (LL95CI) as well as the lower limit of the one-sided 95% prediction interval (LL95PI) were calculated. Following ICH [29], the LL95CI could be used to study stability of a product. However, we used a more stringent definition based on the LL95PI: a solution is considered unstable when 5% of the samples have lost 10% of the initial content.

This analysis was performed using R 4.1.1 (The R Foundation for Statistical Computing, Austria, Vienna, 2021) and the following packages: ggplot2 (for the graphical representation of data), nlme (to fit linear mixed models) and merTools (to compute the confidence and prediction intervals from linear mixed models).

4. Results and discussion

4.1. Development of the quantification method

Gemcitabine has a hydrophilic nature (partition coefficient (log P): − 1.467). Despite the polarity of the molecule, the choice was made to work in reverse phase in order to use a polar mobile phase that remains more stable over the time. In this context, a C18 column was chosen. The pH-dependent distribution of species showed that the neutral form of Gemcitabine was in solution at pH between 4 and 10. Working with the unique neutral form of gemcitabine in solution avoids possible interactions with the residual silanol groups of the column. A working pH of 7 was fixed using a phosphate buffer (Na2HPO4 / KH2PO4, 0.01 M). The organic phase was composed of Acetonitrile (ACN). The mobile phase consisted of phosphate buffer (95%) and ACN (5%), allowing a rapid elution. The column temperature was fixed at 30 °C. Chromatograms were extracted at a wavelength of 275 nm based on the analysis of the molecule spectrum. Several dilutions were tested, and a hundred fold dilution of the sample was finally chosen with an injection volume set at 1 µl.(Table. 2)

4.2. Validation of the quantification method

The results of the method validation are shown in Table 4.

The linearity was confirmed over the range 0.003–15 mg/ml. A range between 3 and 7 mg/ml has been validated in order to quantify the molecule of interest. It provides acceptable precision and accuracy at the extreme values (Table 3). Table 4

For the detection and quantification limits, a blank was injected 10 times and the background noise at the retention time of Gemcitabine was quantified after each injection. The calculation of the mean value gave 0.15023 mg/ml with a standard deviation of 0.000154 mg/ml. LOD and LOQ were then calculated as follows:

- LOD= 0.15023 + 0.000154 * 3 = 0.150692 mg/ml

Table 2
Intra and inter-assay precisions of gemcitabine (n = 10). Precision results are expressed as mean ± SD (relative SD %).

		Expected value	Calculated value
Gemcitabine (mg/ml)	**Intra-assay**	3	3.03 ± 0.01 (0.23)
		5	4.91 ± 0.01 (0.27)
		7	6.81 ± 0.05 (0.72)
	Inter-assay	3	3.01 ± 0.04 (1.19)
		5	5.02 ± 0.07 (1.40)
		7	7.04 ± 0.09 (1.33)

Table 3
Evolution of the optical densities during storage at 5 ± 3 °C and 23 ± 2 °C.

Dose (mg)	Storage temperature (°C)	Optical densities (Mean ± SD)		
		350	410	550
1600	23 ± 2	0.007 ± 0.001	0 ± 0.001	-0.001 ± 0.001
	5 ± 3	0.007 ± 0.001	0 ± 0.001	0 ± 0.001
1800	23 ± 2	0.007 ± 0.001	0 ± 0.000	-0.001 ± 0.001
	5 ± 3	0.008 ± 0.001	0 ± 0.000	0 ± 0.001
2000	23 ± 2	0.008 ± 0.001	0 ± 0.001	0 ± 0.001
	5 ± 3	0.007 ± 0.002	0 ± 0.000	0.001 ± 0.000

- LOQ= 0.15023 + 0.000154 * 10 = 0.15177 mg/ml

Limits of detection and quantification were thus respectively of 0.151 and 0.152 mg/ml, based on a mean background noise of 0.150 mg/ml at the retention time of gemcitabine.

The results of intra and inter-assay precisions are displayed in terms of percentage relative standard deviation for the three levels of control (C1, C2, C3).

The robustness of the method was confirm given that the percentage relative standard deviation for the three levels of control remained under the intra-assay precision when the pH of the mobile phase was varying (Table 5).

The degradation test showed a diminution of the main peak (> 20%) without interfering peak, demonstrating the stability-indicating capability of the method [30] (Fig. 1)

4.3. Stability

4.3.1. Physical stability

The optical densities remained stable at 350, 410 and 550 nm over the 49 days varying from 0 to 0.008 for all concentrations and in the two storage conditions (Table 3). The inspection of the solutions in front of white and black background did not show particles, change of colour or opacity appearance. The microscopic examination of the solution after centrifugation did not highlight crystals.

4.3.2. Chemical stability

The pH remained stable over the study period at 5 ± 2 °C (bags of 1600 mg pH=7.07 ± 0.19; bags of 1800 mg pH=7.06 ± 0.18 and bags of 2000 mg pH=7.08 ± 0.18) as well as at 23 ± 2 °C (bags of 1600 mg pH=7.09 ± 0.12; bags of 1800 mg pH=7.12 ± 0.10 and bags of 2000 mg pH=7.14 ± 0.10)

The peak of interest remained free from interference during the study period for all conditions bags. After each run, the spectrum of gemcitabine was inspected on the PDA detector to insure the purity of the peak.

The concentrations of gemcitabine were stable in the three condition bags for at least 49 days of storage at 5 ± 3 °C and 23 ± 2 °C. In accordance with the predefined criteria, no solution lost more than 10% of its initial concentration (Fig. 2).

4.4. Discussion

Several chromatographic methods have been previously described [31] to measure the gemcitabine concentration as HPLC with an UV detector or HPLC tandem mass. In this study, we develop an UHPLC system coupled to a PDA detector to determine gemcitabine concentrations. This method strictly complied with ICH guidelines and is easier to use than LC-MS/MS systems [12,13] but remained more sensitive and

Table 4
Linearity, limits of detection and quantification, intra- and inter-assay variations and accuracy.

	Linearity			LOD (mg/ml)	LOQ (mg/ml)	Intra-assay (RSD %)	Inter-assay (RSD%)	Accuracy (RSD%)
	Range (mg/ml)	Equation	R^2					
Gemcitabine	0.003–15	y = 0,9405x - 0,0335	0.9996	0.151	0.152	C1: 0.23 C2: 0.28 C3: 0.72	C1: 1.19 C2: 1.40 C3: 1.33	C1: 0.30 C2: 0.38 C3: 0.57

Table 5
Evaluation of the robustness of the method through pH variation of the mobile phase.

pH Mobile Phase	C1 (mg/ml)	C2 (mg/ml)	C3 (mg/ml)
6.75	2,994	4,985	7,011
6.52	3,034	4,988	6,987
6.62	2,987	4,991	7,049
6.5	2,973	4,973	7,004
6.54	2,995	4,989	6,971
Mean	2,997	4,985	7,004
SD	0,023	0,007	0,030
% RSD	0,76	0,14	0,42

stability-indicating than usual HPLC-UV methods [5–7]. It differs from other methods according to the type of system used [32]. The ultra-high pressure brought an improved sensitivity to detect and separate degradation peaks during the degradation test while the use of the PDA detector could measure the entire wavelength range in real time extending the detection of such peaks.

Scientific evidence of the stability of anticancer drugs under specific preparation and storage conditions are required to implement dose-banding safe for the patient. The significant lack of scientific data on the stability of anti-cancer drugs is a major obstacle [33]. Only few references are available in the literature about the long-term stability of gemcitabine in specific conditions. Ponton et al. [8] assessed the stability of lyophilised gemcitabine reconstituted in 0.9% sodium chloride solution (final concentration of 7.5 and 25 mg/ml) in glass bottles and PVC bags at 25 °C. The concentrations of gemcitabine were stable in those conditions for 27 days. The authors didn't investigate the effects of lower temperatures but the risk of crystallisation in cold storage conditions is reported for this anticancer drug [34]. This was confirmed by the works of Xu et al. who studied the physical and chemical stability of hydrochloride salt of gemcitabine after reconstitution under various conditions [9]. They showed the crystallisation of the molecule at a concentration of 38 mg/ml in original vials stored at 4 °C for 14 days or more. In the same study, they assessed the stability of the molecule at concentrations of 0.1 mg/ml and 10 mg/ml in PVC bags at 23 °C and 4 °C for at least 35 days without crystallisation. Considering the risk of

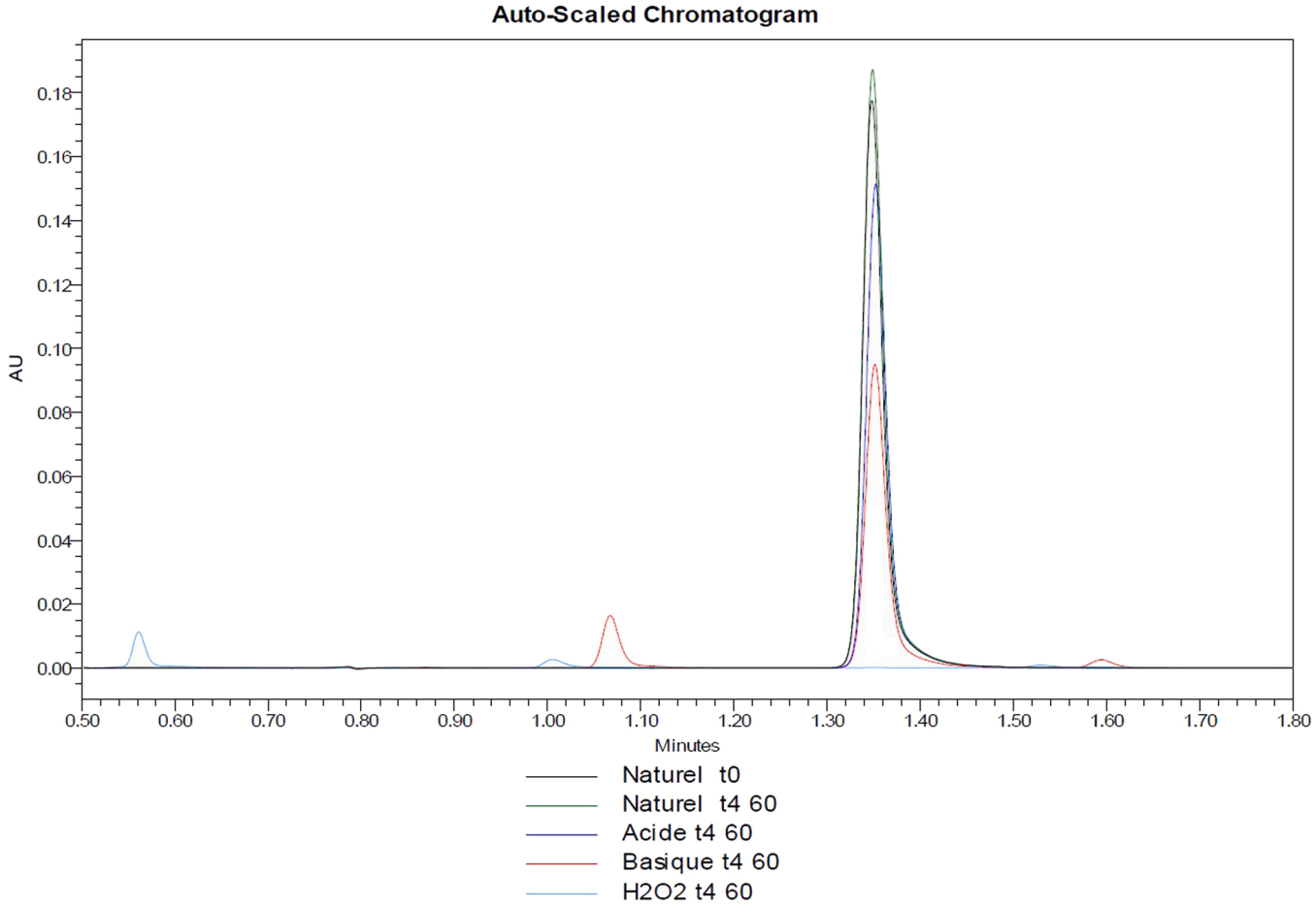

Fig. 1. Forced degradation chromatogram of gemcitabine after 4 days at 60 °C: natural t0 (black), natural t4 (green), acidic t4 (dark blue), alkaline t4 (red), oxidative t4 (light blue).

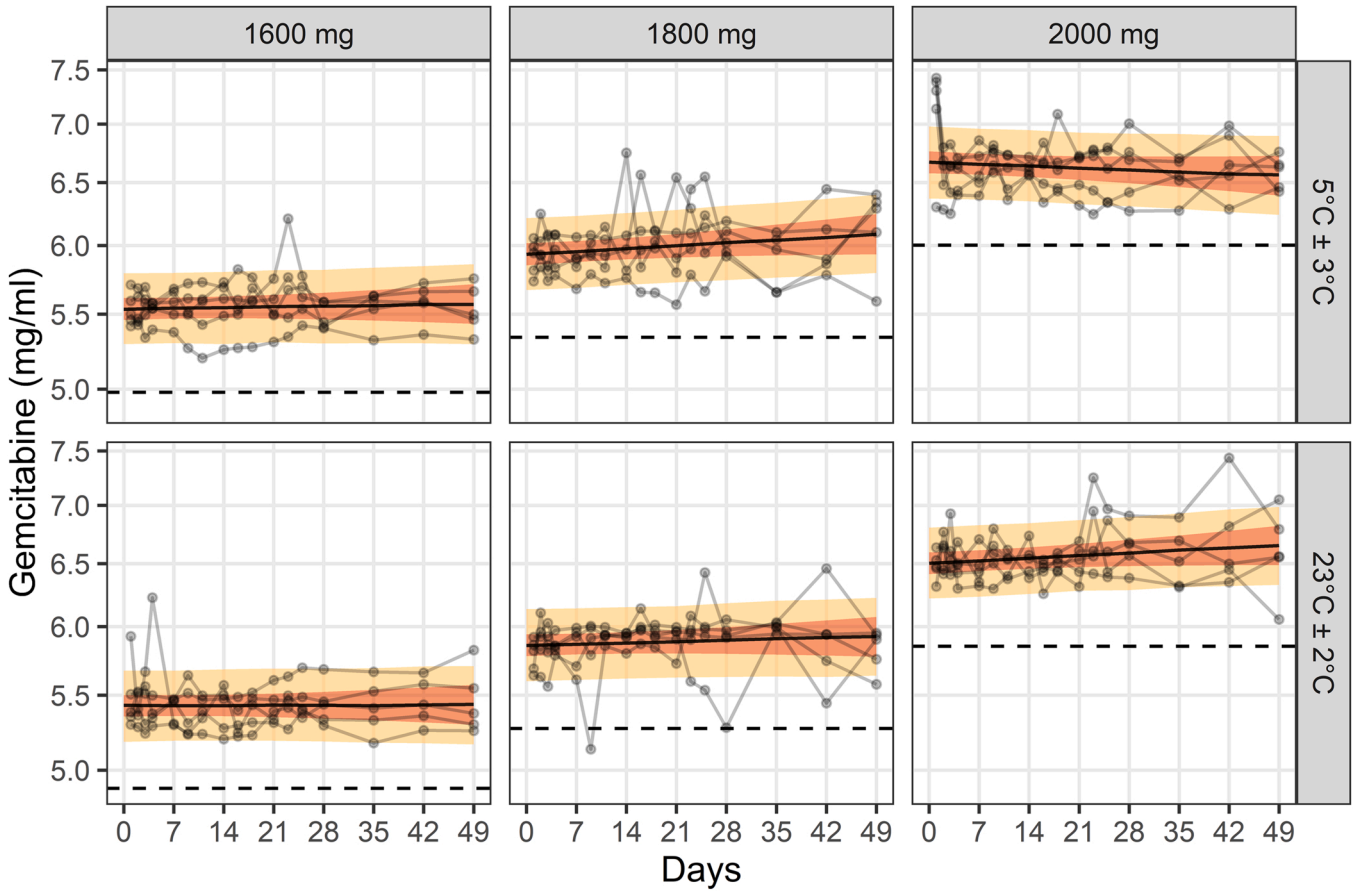

Fig. 2. Evolution of the concentrations of gemcitabine in 1600, 1800 and 2000 mg conditions bags at 5 ± 3 °C and 23 ± 2 °C for 49 days. Grey dots represent observations for each studied syringe. Black line represents the mean estimated by the linear regression. Dashed line represents 90% of the estimated concentration at D0. Red zone defines the limits of the 90% CI and orange zone represents the limits of the 90% prediction interval.

crystallisation in cold storage conditions and the lack of data about the compatibility of gemcitabine in polyolefin bags, it was necessary to evaluate the stability required by the dose-banding conditions specified in our study and commonly used in clinic. Our results showed the physical stability of the molecule with the absence of crystals at lower temperatures attested by microscopic examination during the study period. The chemical stability – based on the stability-indicating method – of gemcitabine in polyolefin bag is confirmed for at least 49 days as deadline of our study.

5. Conclusion

We developed a simple, accurate and stability-indicating UHPLC method to determine gemcitabine concentrations in dose-banding conditions.

This study confirms that gemcitabine in 0.9% sodium chloride solutions at selected standardised rounded doses of 1600 mg/ 292 ml, 1800 mg/ 297 ml and 2000 mg/ 303 ml is chemically and physically stable in polyolefin bags at 5 ± 3 °C and 23 ± 2 °C for at least 49 days. This study supports a centralised production of gemcitabine in accordance with the studied conditions.

Declaration of Competing Interest

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.

Data Availability

Data will be made available on request.

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