Long-term stability of ready-to-use 1-mg/mL midazolam solution

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Purpose. Midazolam is a benzodiazepine derivative commonly used in intensive care units to control sedation. Its use requires dilution of a 5-mg/mL commercial solution to a target concentration of 1 mg/mL. A study was conducted to evaluate the stability of diluted ready-to-use 1-mg/mL midazolam solutions over 365 days when stored in cyclic olefin copolymer vials or polypropylene syringes.

Methods. A specific stability-indicating high-performance liquid chromatography coupled with UV detection method was developed for midazolam hydrochloride and validated for selectivity, linearity, sensitivity, precision, and accuracy. Three storage conditions were tested: –20°C ± 5°C, 5°C ± 3°C, and 25°C ± 2°C at 60% ± 5% relative humidity. Half of the vials were stored upside down to test for the absence of interaction between midazolam and the stopper. Particle contamination, sterility, and pH were assessed.

Results. The limit of stability was set at 90% of the initial concentration. After 1 year's storage at –20°C and 5°C, concentrations remained superior to 90% under all storage conditions. At 25°C, stability was maintained up to day 90 in syringes (mean [SD], 92.71% [1.43%]) and to day 180 in upright and upside-down vials (92.12% [0.15%] and 91.57% [0.15%], respectively). No degradation products were apparent, no variations in pH values were detected, and containers retained their sterility and conformity with regard to any specific contamination during the study.

Conclusion. The evaluated 1-mg/mL midazolam solution was stable over a 1-year period when stored at a refrigerated (5°C) or frozen (–20°C) temperature in both vials and syringes; with storage at 25°C, the stability duration was lower. The preparation of ready-to-use midazolam solutions by a hospital pharmacy is compatible with clinical practice and could help to decrease risks inherent in dilution in care units.

Keywords: infusion, liquid chromatography, midazolam, stability-indicating method

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Midazolam is a benzodiazepine derivative commonly used in intensive care units (ICUs) to control sedation. It is prescribed in preoperative anesthesia for its intensive sedative and hypnotic action and administered intravenously by bolus or continuous infusion, depending on routines adopted in ICUs. In France, injectable midazolam solutions are available at a concentration of 1 mg/mL packaged in 5-mL vials or a concentration of 5 mg/mL in 1-, 3-, or 10-mL vials. These presentations can be used without any preparation step for bolus injection. When administered by continuous infusion, a 1-mg/mL midazolam solution can be prepared by mixing the contents of 5-mL vials or by diluting a 50 mg/10 mL commercial midazolam solution with 0.9% sodium chloride injection in 50-mL polypropylene (PP) syringes. The latter method is cheaper and is recommended in ICUs. Medication errors resulting from manual preparation of injectable solutions are numerous. Multiple dilutions

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by nurses several times a day can result in dilution errors, solvent errors, and sterility disruption.[1-4] These problems may compromise care safety and lead to severe adverse effects,[5-7] especially in ICUs because of the weakness of critically ill patients.[8,9] Standardization of preparations to remedy the lack of industrial products at the appropriate dosage would decrease the risks involved in the dilution step.

To our knowledge there are no published data on the stability of diluted midazolam preparations (1 mg/mL) stored in PP syringes or in cyclic olefin copolymer (COC) vials; there are some published data for injectable midazolam stored in PP syringes at 2-, 3-, and 5-mg/mL concentrations.[10-12] Several methods to analyze midazolam in biological samples have been developed.[13-19]

The study described here aimed to evaluate the long-term stability of diluted, ready-to-use, 1-mg/mL midazolam solutions over 365 days in 2 storage containers: PP syringes and COC vials.

KEY POINTS

- The stability of ready-to-use 1-mg/mL midazolam solution depends on the storage temperature and type of container.
- With storage at ambient temperature, the beyond-use interval for 1-mg/mL midazolam solution compounded in polypropylene (PP) syringes (ie, 90 days after preparation) was shorter than that for solution kept in cyclic olefin copolymer (COC) vials (180 days).
- The stability of ready-to-use 1-mg/mL midazolam solution was maintained in both PP syringes and COC vials for 365 days with storage at –20°C or 5°C.

Materials and methods

Products. Midazolam[a] commercial solution was compounded with excipients such as water for injection, 0.9% sodium chloride injection, hydrochloric acid, and sodium hydroxide to adjust the pH value to 3.3. Ultrapure water (UPW)[b] and sterile 0.9% sodium chloride injection[c] were used to obtain clinical concentrations. A midazolam standard reference[d] used for the validation step was of analytical grade. Diazepam[e] was chosen as an internal standard (IS), and 20 mM acetate buffer,[f] trichloroacetic acid,[g] and acetonitrile[h] were used for the mobile phase; absolute ethanol[i] was used to dissolve midazolam and diazepam.

Syringes were 50-mL PP luer-taper syringes[j]; vials were 50-mL AT-Closed vials[20,k] with a body constructed of COC and a stopper made of thermoplastic elastomer. COC is characterized by high transparency and mechanical resistance.[21] AT-Closed vials are designed to be sterile, clean, closed, and ready-to-fill and meet the required criteria for pharmaceutical primary containers. The filling process was conducted in the same way as described by Feutry et al.[22]

Solution preparations. Quality controls were prepared by dissolving midazolam standard reference (10 mg) in 10-mL graduated flasks with absolute ethanol to obtain 1-mg/mL primary stock solutions.

Midazolam solution for forced degradation (10 µg/mL) was prepared from a 1:100 dilution of an aliquot from the stock solution (1 mg/mL) with UPW and was submitted to high temperature.

Another degradation midazolam solution (40 µg/mL) was prepared by diluting with UPW and then subjected to variations in pH and oxidative conditions according to guidelines jointly issued by the French Society of Clinical Pharmacy (SFPC) and the Group of Evaluation and Research for Protection in Areas Under Control (GERPAC).[23]

Calibration solutions were prepared by diluting stock solutions with UPW to obtain calibration standards at concentrations of 6, 8, 10, 12, and 14 µg/mL.

The concentration of diazepam was determined so that its peak was equivalent to that of the midrange midazolam calibration (7.5 µg/mL).

Solutions used for stability tests were prepared at ambient temperature by diluting commercial midazolam solution with 0.9% sodium chloride injection to reach a concentration of 1 mg/mL. 150 PP syringes were filled manually, and 300 COC vials were automatically filled to the appropriate volume using an automated filling station[l] connected to a peristaltic pump.[m] Dilution of stock solutions with 0.9% sodium chloride injection (from 1 mg/mL to 10 µg/mL) was required for the dosage method.

One hundred fifty COC vials were stored upside down to guarantee contact between the stopper and the solution to determine the impact of the stopper on the stability of the preparation. The other vials were stored upright.

According to the nature of the molecule and respecting SFPC/GERPAC and International Council for Harmonization (ICH) guidelines,[24] 3 storage conditions were tested for each of the 3 container types (syringes, upright vials, and upside-down vials) over 365 days: –20°C ± 5°C, 5°C ± 3°C, and 25°C ± 2°C at 60% ± 5% relative humidity (RH). Each syringe or vial was used for only 1 analysis.

Chromatographic apparatus and conditions. Measurements were made using an ultrafast liquid chromatographic (UFLC) system[n] coupled with a UV detector and equipped with a column[o] maintained at 25°C. The wavelength was optimized between 220 and 254 nm[25] and was finally set at 235 nm to obtain the best sensitivity. The mobile phase, consisting of (A) 20 mM acetate buffer/trichloroacetic acid, with pH adjusted to 3.00, and (B) acetonitrile was run at 65:35 vol/vol, with isocratic elution (0.2 mL/min). An injection volume of 5 µL was used for all analyses. Data acquisition, peak interpretation, and calibration were performed with ChemStation software.[p]

Validation method. The calibration curves were established by

plotting the peak area ratios of the analytes to the IS vs the concentration ratios of the analytes. Analysis of variance (ANOVA) of the linear regression data was performed to assess the significance ($P < 0.05$) of the proposed method. If the nonlinearity ANOVA test was significant, especially because of very low residual variance, the second-degree polynomial test was applied. By verifying that the coefficient of the second degree was not different from 0, the Student's *t* test showed that linear adjustment was the adapted model. Intraday precision and accuracy were assessed through triplicate analyses of the samples at 5 concentrations (6, 8, 10, 12, and 14 µg/mL), and interday precision was evaluated by repeating the analyses on 3 consecutive days. Precision was determined as a coefficient of variation. Trueness was expressed through the recovery factor; accuracy, or the sum of precision and trueness, was displayed as a graph called the accuracy profile. The accuracy profile was computed with a data risk of 5%, and acceptance limits were fixed at ±10%.

Forced degradation study. The specificity of the stability-indicating method was assessed by comparing the chromatograms of midazolam and diazepam quality control solutions with those obtained from forced degradation samples. Degradation of the molecule was provoked by submitting it to the following extreme conditions to obtain about 20% degradation[23]:

- Dilution in hydrochloric acid[q] 0.1N for 10 minutes at ambient temperature, then neutralization with sodium hydroxide[r] 0.1N
- Dilution in sodium hydroxide 0.1N for 10 minutes at ambient temperature, then neutralization with hydrochloric acid 0.1N
- Dilution in 2.25% sodium peroxide solution[s] for 90 minutes at ambient temperature
- Storage in a heated chamber[t] (at 90°C) for 24 hours

To guarantee the selectivity of the study, it was expected that the peaks of degradation products would have retention times different from those of midazolam and diazepam.

Stability profiles were drawn with GraphPad Prism 6 software.[u]

Operating conditions for the stability study. Stability was controlled following SFPC/GERPAC recommendations[23] and ICH guidelines.[24] Midazolam stability was determined on days 0, 1, 2, 3, 4, 7, 14, 21, 28, 60, 90, 180, 270, and 365. At each time point, macroscopic observations were made and midazolam concentrations measured via high-performance liquid chromatography (HPLC) coupled with UV detection for 3 vials stored upright, 3 vials stored upside down, and 3 syringes. Concentrations were expressed as percentages of the initial concentration prepared in the vials. Midazolam hydrochloride was assumed to be stable if the remaining concentration was greater than 90% of the initial concentration, as no degradation product of midazolam is known to be toxic.

Sterility and particulate contamination were tested at the beginning and end of the stability study[23] according to *European Pharmacopeia* specifications[26,27] to ensure that the prepared solutions complied with the quality parameters required for parenteral preparations.[28] Sterility was tested after membrane filtration[v] of the samples. The filters were then incubated in a fluid thioglycolate medium at 35°C and soya bean casein digest medium for 14 days at 22°C. According to *European Pharmacopeia* criteria, preparations with a volume of <100 mL comply with the particulate contamination test if the number of particles measured does not exceed 6,000 particles of ≥10 µm per container and 600 particles of ≥25 µm per container.

Monitoring of pH was conducted with a pH meter[w] at each time point. A nonparametric Kruskal-Wallis *U* test ($\alpha = 0.05$) was used to compare pH results for the 3 groups (upright vials, upside-down vials, and syringes).

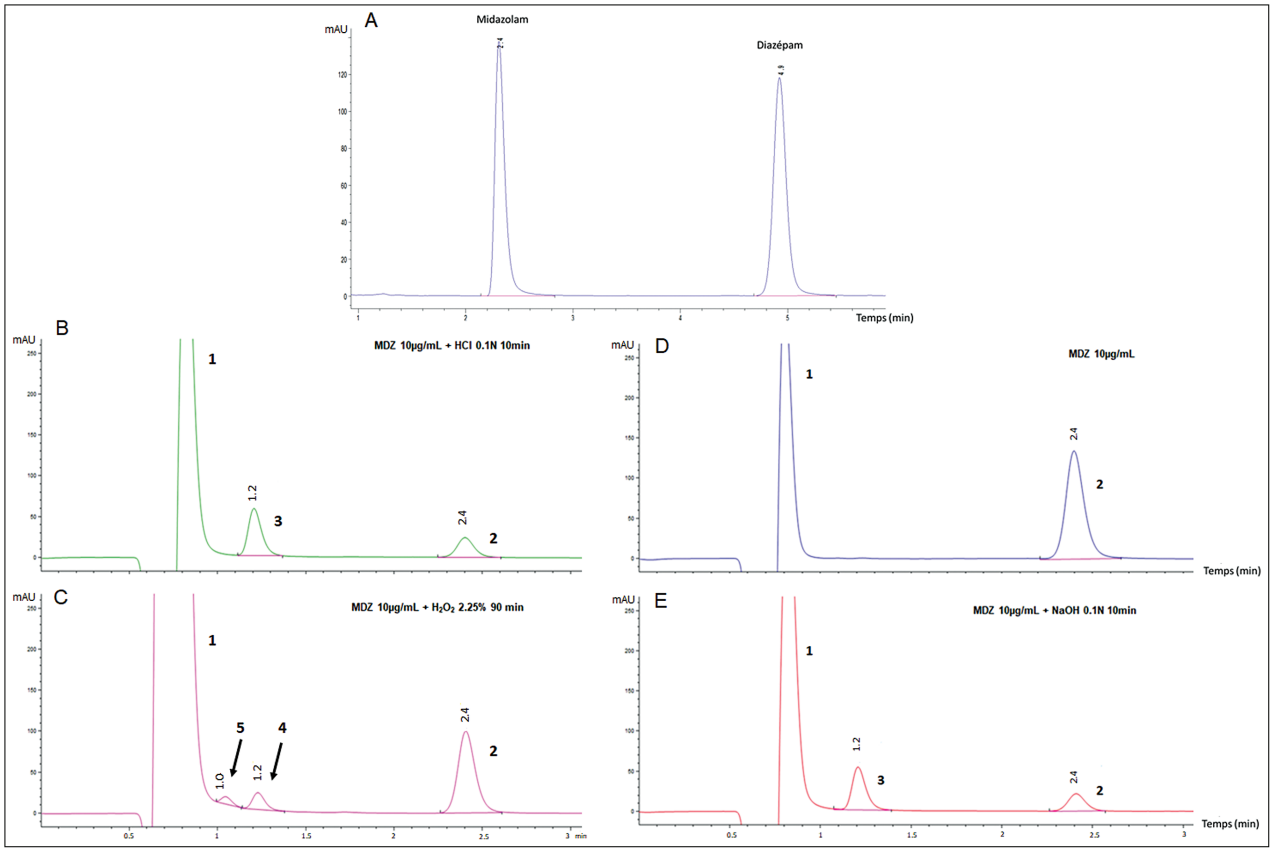
Results

Validation assay and accelerated degradation. The retention times for midazolam and diazepam were 2.4 and 4.9 minutes, respectively (Figure 1A). The symmetry peak factor was acceptable according to *European Pharmacopeia* criteria (symmetry factor, 1.2; reference standards, 0.8-1.5).[29] Representative chromatograms of the degradation products are shown in Figure 1. A degradation product was eluted at a mean of 1.20 (SD [$n = 9$], 0.02) minutes in both acid and basic conditions and was therefore considered as a unique compound. Oxidative degradation led to the formation of 2 different degradation products, respectively eluted at 1.00 (SD [$n = 2$], 0.00) and 1.20 (SD [$n = 6$], 0.01) minutes. The one eluted at 1.20 minutes had the same retention time as the degradation product identified in the acid-based degradation assay and was considered to be the same compound, called degradation product A; the one eluted at 1.0 minutes was called degradation product B. No degradation product appeared to be formed under heating conditions (90°C for 24 hours). The method was shown to be highly selective, with no interference between the molecule (10 µg/mL), which was eluted at 2.4 (SD [$n = 16$], 0.06) minutes, and the degradation product or the IS (7.5 µg/mL), whose retention time was 4.9 minutes.

Calibration results pointed out variance homogeneity (Cochran's test: $C_{exp} = 0.4426 < C_{(5\%;5;8)} = 0.4564$) for midazolam. ANOVA demonstrated an excellent correlation between the ratio of peaks and concentrations ($F_{exp} = 4.29 > F_{(5\%;3;36)} = 2.87$) but showed nonlinearity ($F_{exp} = 1507.16 > F_{(5\%;1;36)} = 4.29$). With the second-degree polynomial test, it is clear that the coefficient of the second degree is not significantly different from 0 ($t_{exp} = 1.37 < t_{(5\%,42)} = 2.01$).

As for the qualification data for the HPLC–UV detection assay performed within the range of 6 to 14 µg/mL, the correlation coefficient was 0.984, with a slope of 0.126 ± 0.003, an intercept of

Figure 1. Chromatograms of the degradation products. mAU indicates milliabsorbance units.



0.040 ± 0.042, a limit of detection of 1.11 µg/mL, and a limit of quantification of 1.21 µg/mL.

Accuracy profiles were validated at 95%, with an acceptance limit of ±10%. Precision results are presented in Table 1. Trueness is represented by total error. The maximal total error obtained for the dosage range was 9.22%.

Our results showed that the linear adjustment method is reliable and adequate for the assessment of physicochemical midazolam stability based on selectivity, linearity, sensitivity, precision, and accuracy.

Table 1. Relative Error, Interday Precision, and Total Error at Calibration Points

Concentration, µg/mL	Relative Bias, %	Interday Precision, %	Total Error, %
6	–2.05	6.33	8.38
8	1.97	5.59	7.56
10	–2.63	4.68	7.32
12	4.53	4.69	9.22
14	–2.26	3.33	5.59

Physicochemical stability. Results for measured midazolam concentrations for the 3 container conditions (syringes, upright vials, and upside-down vials) at the 3 temperature conditions (–20°C ± 5°C, 5°C ± 3°C, and 25°C ± 2°C at 60% ± 5% RH) are presented on Figure 2 and summarized in Tables 2, 3, and 4, respectively.

Freshly prepared solutions were clear, without any visible particles and with an initial mean pH value of 3.40 (SD [n = 3], 0.02). Before storage (day 0), the mean (SD) number of particles of ≥10 µm per container was 4.7 (0.6) for syringes and 67.7 (11.6) for vials, while the number of particles of ≥25 µm was 0.0 (0.0) per syringe and 0.3 (0.6) per vial.

Throughout the stability study, no color modification, precipitation, or visible particles appeared.

At –20°C and at 5°C, the midazolam solution remained stable until the end of the study. The mean (SD) concentrations of midazolam solutions after 1 year were 99.29 (0.85%), 99.19 (0.79%), and 99.01 (0.57%) with storage at –20°C

Figure 2. Measured midazolam concentrations under the 3 storage conditions.

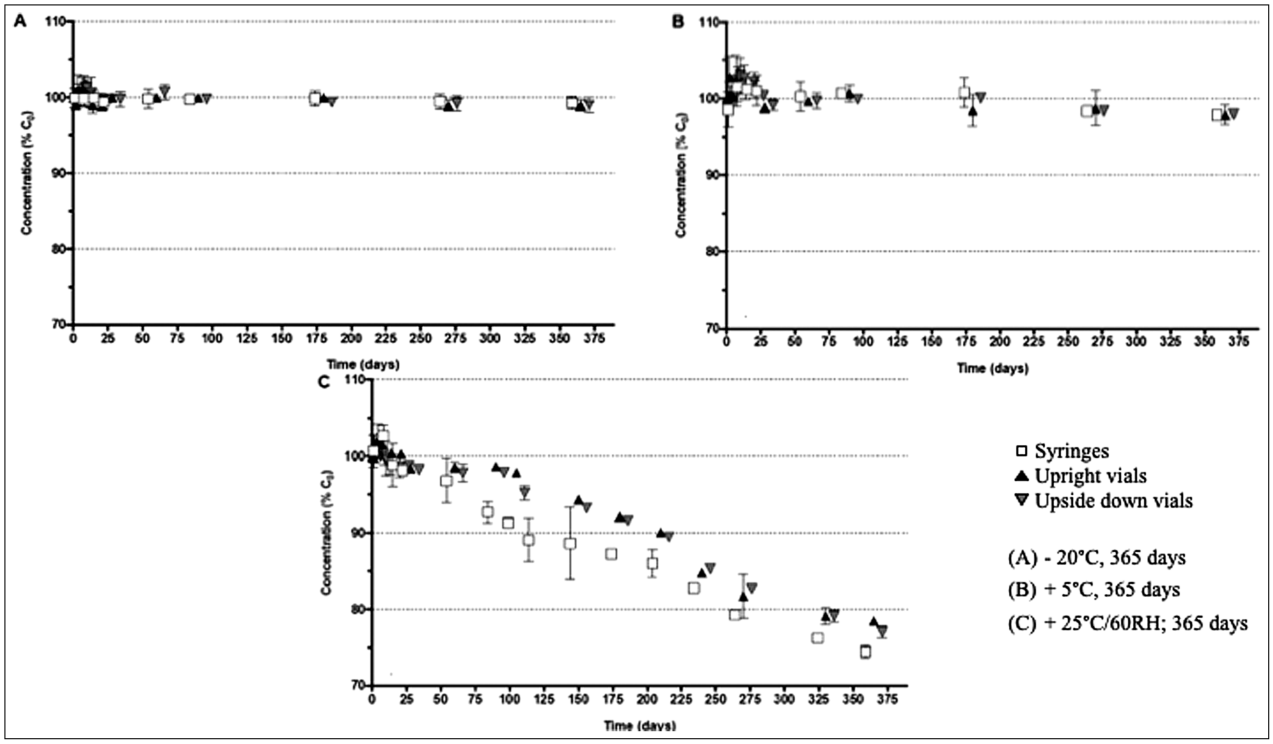


Table 2. Chemical Stability Results for 1-mg/mL Midazolam Solution Stored at –20°C ± 5°C

	% Initial Concentration, Mean (SD)[a]		
Day	Syringes	Upright Vials	Upside-Down Vials
0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)
1	101.75 (0.26)	100.00 (0.37)	99.89 (0.00)
2	102.10 (1.90)	99.08 (0.41)	100.83 (1.74)
3	101.33 (0.27)	101.17 (2.00)	101.36 (1.4)
4	100.88 (0.55)	101.32 (0.82)	101.32 (0.82)
7	99.96 (1.23)	101.40 (1.63)	100.66 (1.84)
14	99.86 (0.95)	99.46 (1.05)	99.57 (0.57)
21	99.92 (1.00)	98.70 (0.67)	99.84 (0.42)
28	99.42 (0.91)	99.63 (0.61)	99.80 (0.63)
60	99.83 (1.28)	99.76 (0.33)	100.75 (1.42)
90	99.80 (0.17)	100.22 (0.23)	99.80 (0.29)
180	99.90 (1.01)	99.75 (0.50)	99.42 (0.17)
270	99.48 (0.98)	99.21 (0.78)	99.25 (0.52)
365	99.29 (0.85)	99.19 (0.79)	99.01 (0.57)

[a]Samples tested in triplicate at all time points.

and 97.89 (0.51%), 97.95 (1.25%), and 98.01 (0.54%) with storage at 5°C for syringes, upright vials, and upside-down vials, respectively. Results showed that when samples were stored in a controlled atmosphere (25°C at 60% RH), stability was maintained up to day 90 in syringes (mean [SD] concentration, 92.71% [1.43%]) and to day 180 in upright and upside-down vials (92.12 [0.15%] and 91.57 [0.15%], respectively).

On day 365, the mean (SD) numbers of particles of ≥10 µm per container were 110 (42), 43 (15), and 43 (13) and the numbers of particles of ≥25 µm were 19 (13), 14 (10), 8 (3), respectively, for syringes, upright vials, and upside-down vials stored at –20°C. With storage at 5°C, the respective mean (SD) numbers of particles of ≥10 µm counted on day 365 were 50 (13), 39 (8), and 46 (9), and the numbers of particles of ≥25 µm were 11 (6), 3 (3), and 4 (5), respectively.

Finally, when samples were stored at 25°C and 60% RH, the mean (SD) numbers of particles counted at the

Table 3. Chemical Stability Results for 1-mg/mL Midazolam Solution Stored at 5°C ± 3°C

	% Initial Concentration, Mean (SD)[a]		
Day	Syringes	Upright Vials	Upside-Down Vials
0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)
1	98.74 (0.05)	100.28 (0.25)	102.44 (0.15)
2	100.83 (2.23)	102.82 (2.72)	101.85 (2.21)
3	100.52 (1.82)	100.40 (1.22)	102.51 (1.64)
4	100.79 (2.14)	100.40 (1.22)	102.99 (2.36)
7	98.64 (2.20)	102.33 (3.38)	102.72 (1.60)
14	101.54 (0.59)	101.30 (1.36)	102.23 (1.28)
21	101.25 (0.60)	101.19 (1.18)	100.43 (0.44)
28	101.06 (1.98)	98.90 (0.40)	99.20 (0.77)
60	100.30 (1.96)	99.65 (0.37)	99.72 (1.04)
90	100.71 (0.20)	100.75 (1.10)	99.91 (0.37)
180	100.81 (1.92)	98.51 (2.04)	100.08 (0.27)
270	98.42 (0.12)	98.79 (2.25)	98.45 (0.21)
365	97.89 (0.51)	97.95 (1.25)	98.01 (0.54)

[a]All samples tested in triplicate at all time points.

deadline for stability testing were 18 (9), 24 (7), and 11 (7) for particles of ≥10 µm and 3 (3), 0 (0), and 2 (4) for particles of ≥25 µm.

Every vial and syringe retained its sterility until the deadline for physicochemical stability testing. After 365 days, mean (SD) pH values were 3.45 (0.01), 3.43 (0.01), and 3.44 (0.02) with storage at –20°C and 3.52 (0.01), 3.52 (0.01), and 3.49 (0.02) with storage at 25°C and 60% RH, for samples kept in syringes, upright vials, and upside-down vials, respectively. Finally, the mean (SD) pH was 3.45 (0.01) for samples in every container type after 365 days with storage at 5°C. The pH values were not significantly modified from initially measured values (in all comparative conditions [$n = 3$], $P \geq 0.1$) during our stability-indicating HPLC–UV assay.

Discussion

A stability-indicating HPLC–UV method to determine the chemical stability of injectable midazolam solutions has been developed and validated. The results of the study indicate that a 1-mg/mL midazolam solution prepared by diluting a 50 mg/10 mL commercial midazolam solution in 0.9% sodium chloride injection is stable for 365 days at both –20°C and 5°C when stored either in PP syringes or in COC vials and, at 25°C and 60% RH, for 90 days in PP syringes and 180 days in COC vials.

Our study was, to our knowledge, the first to evaluate the stability of 1-mg/mL ready-to-use midazolam solutions in COC vials and in PP syringes. The storage of frozen solutions has not yet been assessed and reported. Maximum stability should theoretically be obtained through freezing, but the problem of defrosting conditions remains (test samples were thawed over 4 hours at room temperature in our study). Several studies have validated the use of microwaves for defrosting.[30-32]

At 5°C, midazolam remained stable for 365 days in both containers, whatever the vial position (upright or upside down). Several studies have already evaluated the stability of midazolam in similar storage conditions (ie, diluted with 0.9% sodium chloride injection and packaged in PP syringes) but with a higher drug concentration and with storage over a shorter period[10] or with storage in polyvinyl chloride bags), with stability maintained up to 30 days.[33,34] A stability analysis of 1-mg/mL midazolam solution stored at 5°C in polyolefin bags showed similar results.[34]

In the literature,[10,11] stability was maintained for 10 days for 2-mg/mL midazolam solutions, 7 days for 3-mg/mL solutions, and for 36 days when 5-mg/mL solutions were stored undiluted at room temperature in PP syringes.[12] None of these studies pursued analyses beyond the end date originally envisaged. Long duration was therefore one of the strong points of our study.

The originality of our study laid in the use of AT-Closed vials, commercial vials designed to be ready-to-fill and meeting the requirement criteria for pharmaceutical primary containers per both *United States Pharmacopeia* and *European Pharmacopeia* standards. Our results attest to midazolam stability duration being greater in COC AT-Closed vials than in PP syringes at room temperature (180 days vs 90 days) and suggest that contact with the stopper does not have any impact, since results were similar whatever the storage position of the vials. These results comply with the declared properties of AT-Closed vials[20-22] and contribute to evidence favoring their use in hospital pharmacy practice.

The UFLC system provided high speed and selectivity on a fast gradient, enabling us to perform fast analyses appropriate for routine use. No stability-indicating HPLC–UV assays for midazolam detection and quantification reported in literature[25,35,36] used an ultrafast HPLC system to optimize the duration of analysis.

A unique compound was formed via the degradation of midazolam in acido-basic conditions. This is consistent with a previous study.[19] Bianchi et al[37] previously noted that in acid conditions

Table 4. Chemical Stability Results for 1-mg/mL Midazolam Solution Stored at 25°C ± 2°C at 60% ± 5% Relative Humidity

	% Initial Concentration, Mean (SD)[a]		
Day	Syringes	Upright Vials	Upside-Down Vials
0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)
1	101.51 (1.65)	99.89 (0.37)	100.64 (0.19)
2	101.17 (1.60)	101.05 (1.86)	100.34 (0.14)
3	101.79 (1.19)	101.07 (1.29)	99.84 (1.01)
4	101.79 (0.71)	101.99 (2.28)	99.78 (2.23)
7	100.69 (2.09)	101.57 (1.40)	98.74 (1.06)
14	102.71 (1.45)	100.43 (0.55)	98.76 (1.50)
21	98.90 (2.84)	100.35 (0.64)	98.85 (0.63)
28	98.24 (0.26)	98.49 (0.59)	98.30 (0.53)
60	96.86 (2.83)	98.65 (0.70)	97.84 (1.15)
90	92.71 (1.43)	98.76 (0.53)	97.90 (0.44)
120	89.11 (2.84)	97.89 (0.35)	95.24 (0.97)
150	88.64 (4.73)	94.38 (0.14)	93.27 (0.28)
180	87.25 (0.61)	92.12 (0.15)	91.57 (0.15)
210	85.99 (1.81)	90.07 (0.11)	89.48 (0.18)
240	82.78 (0.40)	84.78 (0.16)	85.33 (0.21)
270	79.24 (0.48)	81.72 (2.91)	82.69 (0.57)
330	76.25 (0.34)	79.15 (1.12)	79.12 (0.75)
365	74.48 (0.84)	78.51 (0.59)	77.01 (0.79)

[a]All samples were tested in triplicate at all time points.

(pH of around 3.40), the closure of the aromatic cycle decreased, the chemical structure was more hydrophilic and soluble, and the risk of interaction with the polymer was minimized.[37] The structure of this degradation product is a benzophenone open ring, first detected by Andersin et al.[38]

It is believed that the closed-ring form of benzodiazepines is the only pharmacologically active form. However, no published study supports any possible toxicity of this form.[39]

Neutralization of the basic medium by hydrochloric acid during the degradation study could be responsible for its formation, which is described as occurring mainly in acid conditions in the literature,[38-41] and these researchers also neutralized their degradation samples.[19]

Degradation products obtained in oxidative conditions are consistent with the results of Feng et al.[19]

A degradation product was detected from day 90 in PP syringes and day 180 in AT-Closed vials with storage at 25°C and 60% RH and was eluted at 1.22 and at 1.16 minutes, respectively. According to elution time, it was identified as the open-ring hydrolytic product of midazolam. Higher pH values were noted when test samples were stored at ambient temperature, with mean (SD) values reaching 3.53 (0.01) in PP syringes and 3.51 (0.01) in COC vials; in comparison, pH values did not exceed 3.48 (0.01) when samples were stored either frozen or at 5°C. This finding suggests that an insignificant modification in pH value might induce the hydrolysis of the closed-ring form.

An interlaboratory assay would be a worthwhile follow-up to assess the reproducibility of our method.

The use of COC vials confers many advantages. It is an innovative process for hospital pharmacies that requires technological equipment, good manufacturing processes, and time-demanding organization. During the study period, as we encountered no loss of stability when midazolam was stored at 5°C or –20°C regardless of the container, we did not determine beyond-use dates for these 2 storage conditions. However, analyses were not pursued beyond the date initially planned for the study, as a 365-day period is reflective of routine use at our institution.

Conclusion

A 1-mg/mL injectable midazolam solution was shown to be stable for at least 1 year when stored at –20°C or 5°C in PP syringes or in COC vials. At room temperature, the solution was stable for 90 days in PP syringes and 180 days in COC vials. Thanks to this long-term stability, the preparing of ready-to-use solutions by a hospital pharmacy is compatible with routine practice and should help to decrease the risks involved in multiple dilutions in ICUs.

Disclosures

The authors have declared no potential conflicts of interest.

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[a]Hydrochloride midazolam injection (50 mg/10 mL), Mylan, Paris, France, lot F30631.

[b]ELGA LabWater, Veolia Water, Antony, France.

[c]Viaflo, Baxter, Maurepas, France, lot 16F28G60.

[d]Sigma Aldrich Chimie, Saint Quentin Fallavier, France, lot 001WA4.

[e]Cooper, Melun, France, lot 11120133A.

[f]Sodium acetate trihydrate, Merck, Fontenay-sous-Bois, France.

[g]Trichloroacetic acid, Merck, Fontenay-sous-Bois, France.

[h]Acetonitrile HiPerSolv Chromanorm, Fontenay-sous-Bois, France.

[i]VWR International, Fontenay-sous-Bois, France.

[j]Plastipak Luer-Lok, Becton Dickinson, Le Pont de Claix, France.

[k]Aseptic Technologies, Gembloux, Belgium.

[l]M1 Filling Station, Aseptic Technologies.

[m]Flexicon Pump PF6, Watson Marlow, La Queue Lez Yvelines, France.

[n]Agilent 1290 Infinity LC, Agilent, Les Ulis, France.

[o]Kinetex Biphenyl (100 Å, 50 · 2.1 mm), Phenomenex, Le Pecq, France.

[p]OpenLab CDS, version 01.05, Agilent.

[q]Hydrochloric acid 37%, Merck KGaA, Darmstadt, Germany.

[r]Hydroxide sodium, Cooper, Melun, France.

[s]Hydrogen peroxide 10 vol., Laboratoire Gilbert, Hérouville Saint-Clair, France.

[t]Binder ED 115, Binder GmbH, Tuttlingen, Germany.

[u]GraphPad Software Inc, La Jolla, CA.

[v]0.45 mm cellulose nitrate filter, Sartorius Stedim Biotech, Göttingen, Germany.

[w]Hanna HI 223 pH Meter, Hanna Instrument, Ann Arbor, MI.

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