Physical and Chemical Stability of Pharmaceutical Preparation of Bumetanide and Scopolamine

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Abstract

Death rattle, which could often be associated with a pulmonary fluid overload, occurs in 25% to 90% of dying patients. The co-administration of scopolamine (anticholinergic drug) and bumetanide (loop diuretic) could be considered in order to avoid unnecessary fluid overload at end-stage of life. The objective of this study was to investigate the physical and chemical stabilities of the admixture bumetanide and scopolamine in order to prepare them in advance by a centralized intravenous additive service in-hospital pharmacy. The stability of the lowest (LOW) concentration was evaluated on five polypropylene syringes containing the admixture bumetanide (Burinex, 2 mg/4 mL) and scopolamine (0.25 mg/mL) at 41.67 µg/mL and 5.21 µg/mL. The highest (HIGH) concentration with 125 µg/mL of bumetanide and 31.25 µg/mL of scopolamine was evaluated on five polypropylene syringes. All syringes were stored for 18 days at 5°C ± 3°C. Periodic samples were visually and microscopically examined to observe any particle appearance or color change. The pH and absorbance at 3 wavelengths (350 nm, 410 nm, and 550 nm) were monitored. The concentrations were measured by ultra-high-performance liquid chromatography–photodiode array detection, using a newly developed method. During the 18 days of test, there was no change in color or appearance of opacity, turbidity, or precipitation, and the pH remained stable. Mean concentrations of bumetanide and scopolamine at LOW and HIGH concentrations after 18 days remained statistically unchanged. The lower limits of the 95% confidence intervals of both molecules at LOW and HIGH concentrations remained higher than a 90% threshold of concentration thus considering the mixture chemically stable. Degradation rates of bumetanide and scopolamine content at LOW and HIGH concentration should not exceed a maximum of 0.70% every 10 days. This study was the first one to show that the admixture of bumetanide and scopolamine is physically and chemically stable at two concentrations used in a palliative-care unit. This combination available in ready-to-use polypropylene syringes presents numerous advantages for patient's comfort and safety.

Introduction

Death rattle, which could be due to excessive mucus accumulation in the respiratory tractus in the absence of effective reflexes in swallowing and coughing, is a frequent clinical sign in the terminal stage of life that occurs in 25% to 90% of dying patients.[1-3] In addition to the non-pharmacological measures in order to improve the patient's comfort, such as the semiprone position to encourage postural drainage or gentle nasopharyngeal or tracheal suction, anticholinergic drugs competitively antagonize acetylcholine at muscarinic receptors and have been used to treat this condition by inhibiting the production of respiratory tract secretions.[1,2] However, anticholinergics do not affect existing mucus. Among them, scopolamine hydrobromide is a tertiary amine with central (e.g., sedation, antiemetic) and peripheral actions.[1,4]

A component of pulmonary fluid overload is often found in patients at end-stage of life and intravenous (IV) loop diuretics, including bumetanide, which are the cornerstones of decongestion in patients with acute heart failure.[5] They increase sodium excretion by up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy, unless renal function is severely impaired.[6] The loop diuretics act by

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inhibition of the sodium-potassium-chloride symporter present in the thick ascending limb of the loop of Henle causing an inhibition of sodium reuptake.[7]

In order to limit fluid overload in end-stage of life patients, co-infusion of scopolamine and bumetanide through previously prepared polypropylene syringes can be considered in the palliative-care unit. After a literature review of physicochemical stability,[8-10] it appears that concomitantly admixture of scopolamine and bumetanide have never been studied before in any condition.

The objective of this study was to investigate the physical and the chemical stabilities of the admixture scopolamine and bumetanide in polypropylene syringes prepared in advance under aseptic condition by a centralized intravenous additive service (CIVAS) in the hospital pharmacy department[11] and stored at 5°C ± 3°C during 18 days.

Materials and Methods

PREPARATION OF ADMIXTURES

Five polypropylene syringes (Lot 1911727; Becton Dickinson, Franklin Lakes, New Jersey) containing the mixture at the lowest (LOW) concentration were prepared under aseptic conditions by adding 4 mL of bumetanide (Lot F1028BE2, Burinex, 2 mg/4 mL; LEO, Lier, Belgium) and 1 mL of scopolamine (Lot 190097, 0.25 mg/mL; Sterop, Brussels, Belgium) to NaCl 0.9% (Lot 20A02E3E, Viaflo 500 mL; Baxter, Lessines, Belgium) 48 mL as directed. Five polypropylene syringes containing the highest (HIGH) concentration were prepared by adding 12 mL of bumetanide and 6 mL of scopolamine to NaCl 0.9% 48 mL as directed. **TABLE 1** summarizes the LOW and HIGH concentrations.

STABILITY STUDY DESIGN

All syringes were stored at 5°C ± 3°C for 18 days and periodically analyzed (after 0, 1, 2, 4, 7, 9, 11, 14, 16, 18 days). At each time point, physical stability was assessed immediately on aliquots of 0.5 mL, while aliquots of 100 µL in triplicate were stored at -80°C for further chemical analyses.

PHYSICAL STABILITY

Aliquots of 0.5 mL were visually inspected on black and white backgrounds for the detection of particle, haze, precipitation, and color change. The crystal formation was microscopically verified with a Jenamed microscope (Carl Zeiss, Oberkochen, Germany) at a magnification x80 after centrifugation at 2.150 g for 5 minutes. In addition, the turbidity was evaluated by spectrophotometric measurements (Genesys 10 Series; Thermo Fischer Scientific, Fitchburg, Wisconsin) at three wavelengths (350 nm, 410 nm, and 550 nm),[12] and the pH was monitored with a glass electrode pH-meter (Inolab Level 1; WTS GmbH & Co., Weilhem, Germany) with a BioTrode electrode (Hamilton Bonaduz AG, Graubünden, Switzerland).

CHEMICAL STABILITY

Chromatographic Assay

Bumetanide and scopolamine concentrations were measured by ultra-high-performance liquid chromatography (UHPLC), Acquity UPLC H-Class; Waters Corporation, Milford, Massachusetts) coupled with a photodiode array (PDA) detector (ACQUITY UPLC PDA eλ Detector, #F13 UPL 741 A; Waters Corporation, Milford, Massachusetts). Data were acquired and processed by the Empower3 software (Waters Corporation). The separation was performed on a reverse-phase column (Lot H16-356030, Luna Omega polar C18 1.6 µm 100 Å, LC column 100 x 2.1 mm; Phenomenex, Utrecht, Netherlands). An elution gradient was carried out with water adjusted to pH 2.5 with phosphoric acid (H_3PO_4) 85% (Lot Z0542328 847; Merck, Overijse, Belgium) and acetonitrile (Lot 1332661; Biosolve, Dieuze, France). The run started with 15% of organic phase for 1.5 minutes before being gradually increased to 70% in one minute. These percentages of organic phase were maintained for 2.5 minutes. The column was re-equilibrated with 15% of organic phase for 2 minutes before the next run. The flow rate was fixed at 0.4 mL/min. Samples were injected two times in order to detect, first, bumetanide (column temperature 30°C, injection volume 1 µL and detection wavelength 227 nm) and then scopolamine (40°C, 10 µL, 220 nm). Both molecules could not be quantified in the same run due to their concentration differences in samples.

TABLE 1.

CONCENTRATIONS IN BUMETANIDE AND SCOPOLAMINE.

	LOW	HIGH
Bumetanide (µg/mL)	41.667	125
Scopolamine (µg/mL)	5.208	31.25

STANDARD AND CONTROL SOLUTIONS

A calibration curve was performed each day of UHPLC analysis based on 5 calibrator solutions (1/X weighted regression procedure), and three controls were used (**TABLE 2**). All solutions were prepared from a fresh admixture of bumetanide and scopolamine.

VALIDATION OF THE ULTRA-HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

The developed method was evaluated according to the International Conference on Harmonization (ICH) guidelines Q2 (R1),[13] including an evaluation of the following characteristics:

Linearity

The range of linearity of analytical response was determined by a two-fold serial dilution (a total of 14 dilutions) from 300 µg/mL to 0.03 µg/mL for bumetanide and from 100 µg/mL to 0.01 µg/mL for scopolamine.

Precision

Within-run variation was evaluated by the relative standard deviation (RSD) of 10 successive injections of the same sample, while between-run variation was determined by the injection of 10 samples prepared on different days. Both within and between-run variations were evaluated on the three levels of controls.

Limits of Detection and Limits of Quantification

Injectable water (Lot 192628091; B. Braun, Melsungen, Germany) was injected 10 times as blank to calculate the limits of detection (LOD) and limits of quantification (LOQ), as follows:

LOD = mean of blank + 3*standard deviation (SD)

LOQ = mean of blank + 10*SD.

Stability-indicating Capability

Forced degradation of samples was performed to evaluate the stability-indicating capability of the method. Main peaks were observed to verify their decrease in case of degradation and the possible interference with the degraded products.[14] The test was performed on fresh admixtures of bumetanide and scopolamine corresponding to LOW and HIGH concentrations and on pure solutions containing only bumetanide (125 µg/mL) or scopolamine (31.25 µg/mL). Vials containing the solutions (1 mL) were treated with 100 µL of aqua for injection (natural condition), 50 µL of hydrochloride (HCl) 2 M (acidic condition), 50 µL of NaOH 2 M (basic condition), or with 100 µL of H_2O_2 30% (w/w) (Lot STBH5484; Sigma-Aldrich, Overijse, Belgium) (oxidative condition). Samples were immediately analyzed and after 4 days at room temperature or at 60°C. They were neutralized with 50 µL of NaOH 2 M or HCl 2 M before the UHPLC injection.

TABLE 2.

CALIBRATORS AND CONTROLS CONCENTRATIONS.

	BUMETANIDE (µG/ML)	SCOPOLAMINE (µG/ML)
Calibrator 1	20	2.5
Calibrator 2	50	6.25
Calibrator 3	80	15.625
Calibrator 4	125	25
Calibrator 5	200	50
Control 1	25	5
Control 2	100	12.5
Control 3	156.25	39.06

TABLE 3.

VALIDATION CRITERIA: LINEARITY, LIMIT OF DETECTION, AND LIMIT OF QUANTIFICATION.

	LINEARITY			LIMIT OF DETECTION (µG/ML)	LIMIT OF QUANTIFICATION (µG/ML)
	RANGE (µG/ML)	EQUATION	R^2		
Bumetanide	1.172 – 300	y = 0.9735x + 0.5339	0.9999	0.372	1.142
Scopolamine	1.563 – 100	y = 0.9865x + 0.0661	1	0.014	0.035

TABLE 4.

INTRA-VARIATIONS AND INTER-VARIATIONS OF MORPHINE AND CLONIDINE (N=10).

	INTRA-ASSAY (*n*=10)			INTER-ASSAY (*n*=10)		
Bumetanide (µg/mL)	24.808 ± 0.026 (0.1)	99.917 ± 0.19 (0.2)	153.449 ± 0.264 (0.2)	25.06 ± 1 (3.9)	101.7 ± 4.2 (4.2)	150.5 ± 5.6 (3.7)
Scopolamine (µg/mL)	5.125 ± 0.03 (0.6)	12.182 ± 0.05 (0.4)	39.29 ± 0.03 (0.1)	5.01 ± 0.06 (1.3)	12.7 ± 0.3 (2.4)	38.6 ± 2.2 (5.6)

CHEMICAL STABILITY STUDY

All aliquots withdrawn at predefined time points from one syringe were thawed at room temperature and analyzed during the same chromatographic run. Samples were injected by the UHPLC system without any previous dilution and analyses were performed in triplicate.

STATISTICAL ANALYSIS

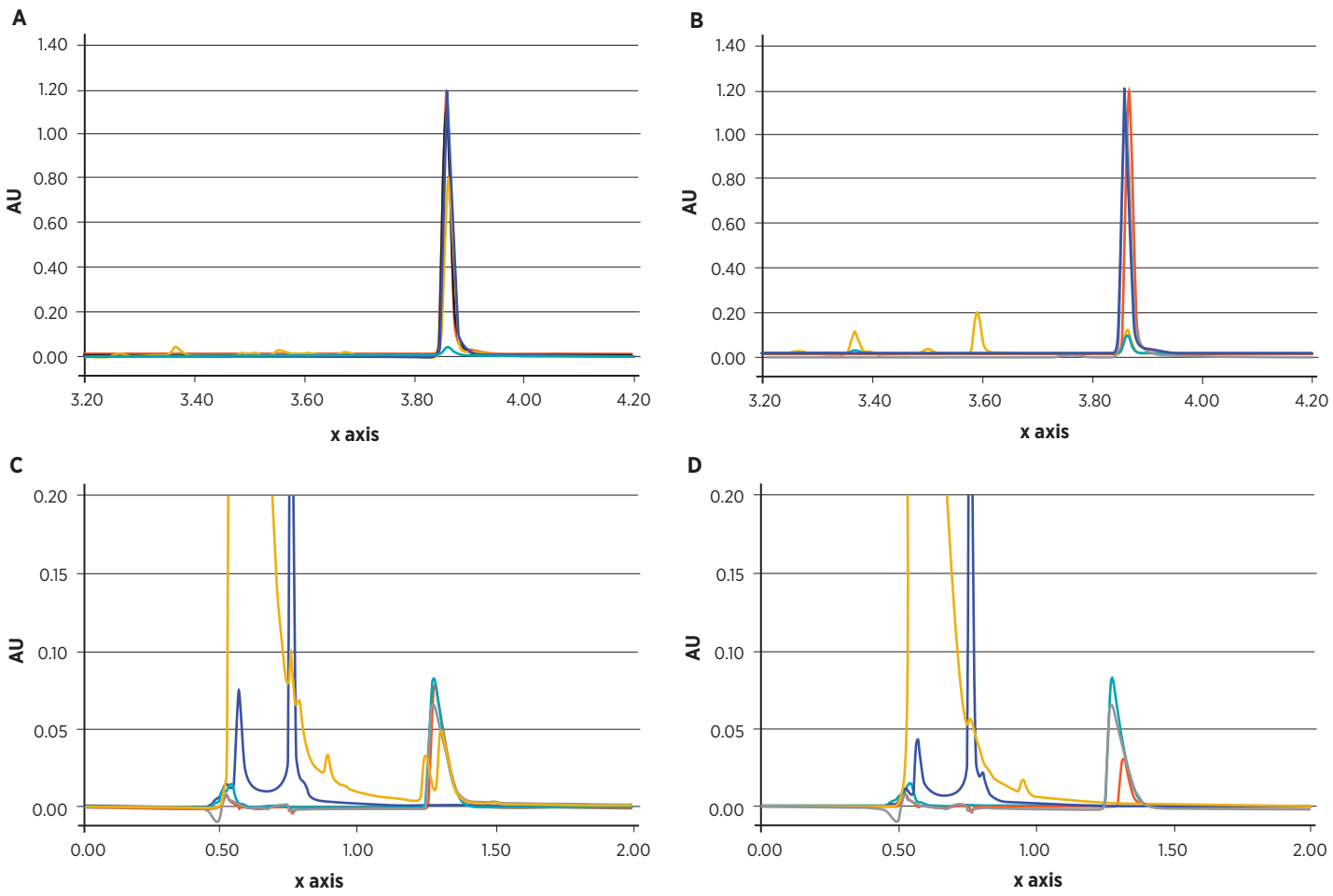
According to ICH Q1E guidelines,[15] pharmaceutical solutions are considered chemically stable while the lower limit of the 95% confidence interval on the mean remains superior to 90% of the initial concentration.

For each syringe, the initial concentration was defined as the intercept of the slope representing the linear evolution of product concentration over time and was computed through linear models.

The degradation rate for both molecules was evaluated. The relative concentrations of the same condition were then combined in order to measure the mean slope of the relative concentration through a linear model. Statistical analyses were performed using R 3.3 (The R Foundation for Statistical Computing, Austria, Vienna, 2017).

FIGURE 1.

EVALUATION OF STABILITY-INDICATING CAPABILITY OF THE METHOD BY FORCED DEGRADATION AT DAY 4 IN DIFFERENT CONDITIONS.



Bumetanide at room temperature (A) and at 60°C (B). Scopolamine at room temperature (C) and at 60°C (D). Chromatogram in grey = natural condition at day 0; in orange = natural condition; in turquoise = acidic condition; in dark blue = basic condition; and in yellow = oxidative condition.

Results

PHYSICAL STABILITY

The admixtures at LOW concentration (bumetanide: 41.67 µg/mL, scopolamine: 5.21 µg/mL) and HIGH concentration (bumetanide: 125 µg/mL, scopolamine: 31.25 µg/mL) appeared physically stable throughout the study period. No pH shift was observed for the LOW concentration (mean ± SD: 6.64 ± 0.05) and for the HIGH concentration (mean ± SD: 6.67 ± 0.06).

Visual examination against black and white backgrounds did not reveal any color change or development of aggregates. The absence of turbidity was confirmed by spectrophotometric measurements at 350 nm (LOW: 0.263 ± 0.001 and HIGH: 0.790 ± 0.001), at 410 nm (LOW: 0.003 ± 0.000 and HIGH: 0.000 ± 0.000) and at 550 nm (LOW: 0.000 ± 0.000 and HIGH: 0.000 ± 0.000). During the 18 days of storage, aggregate formation was not observed in LOW and HIGH concentrated solutions by light microscopy.

ULTRA-HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD DEVELOPMENT

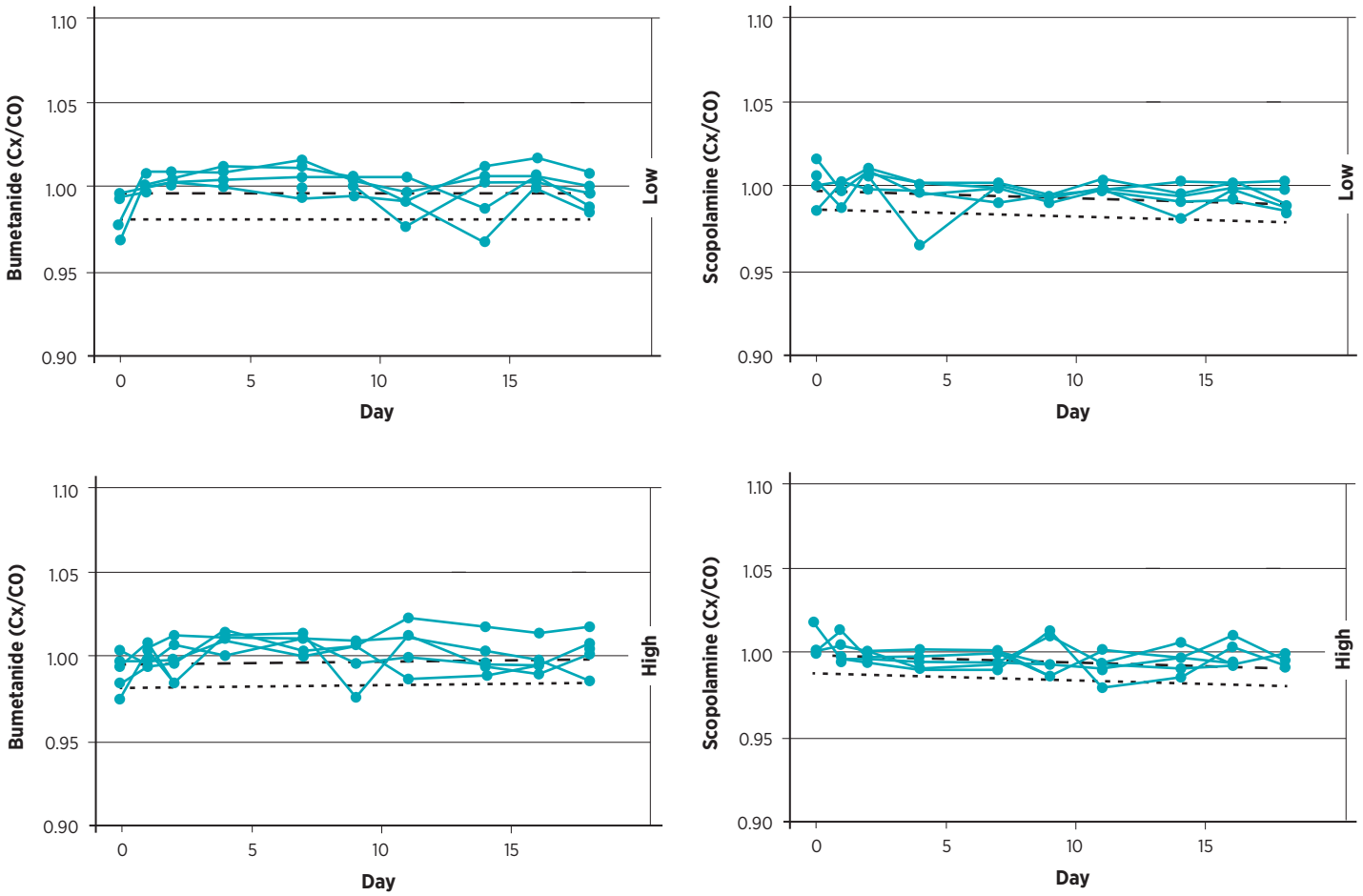
A C18 column was chosen based on the hydrophobic profile of the two components (partition coefficient [logP]: 2.42 for bumetanide and 0.89 for scopolamine). The pH-dependent species distribution

shows that only a basic pH above 12 allows to analyze unique species for both bumetanide and scopolamine. However, this range of pH was not chosen to avoid potential hydrolysis of the column surface. The compromise between the pH-dependent species distribution and the pH supported by the column was to perform the analysis at acidic pH.

pH 2.5 was selected in order to neutralize residual silanols and to limit secondary interactions with charged species. Unfortunately, 60% of positive-charged bumetanide coexist with 40% of neutral bumetanide at this pH, but the evaluation of between-run variation showed that our UHPLC method was reproducible anyway and the peak shape was suitable. Water was adjusted to pH 2.5 with phosphoric acid 85% and an elution gradient with acetonitrile was performed. The flow rate was fixed at 0.4 mL/min, corresponding at a good agreement between a fast analysis and a decrease of peaks tailing. Several injection volumes of samples were tested before choosing an injection of 1 µL for bumetanide and of 10 µL for scopolamine, both without any dilution. Suitable retention times for molecules of interest were achieved with temperature columns of 30°C for bumetanide detection and 40°C for scopolamine detection. According to the molecules spectra, chromatograms were extracted and quantified at 227 nm (bumetanide) and at 220 nm (scopolamine) to ensure suitable absorption without solvent interference.

FIGURE 2.

RELATIVE CONCENTRATION EVOLUTION OVER TIME FOR BUMETANIDE (LEFT) AND SCOPOLAMINE (RIGHT).



C0 = initial concentration in bumetanide or scopolamine; Cx = concentration in bumetanide or scopolamine at day X. Grey lines represent observations for each studied syringe. Black line represents the mean estimated by the linear regression. Dashed line represents the lower limit of the one-sided 95% confidence interval. Dotted line represents the lower limit of the one-sided 95% prediction interval.

ULTRA-HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY VALIDATION METHOD

The analytical response was linear between 1.172 µg/mL and 300 µg/mL for bumetanide quantification and between 1.563 µg/mL and 100 µg/mL for scopolamine quantification. LOD and LOQ for bumetanide and scopolamine are reported in **TABLE 3**. The within-run and between-run variations (n=10 for each) were evaluated on the three levels of controls (**TABLE 4**).

FIGURE 1 presents the forced degradation chromatograms after 4 days at room temperature (A and C), at 60°C (B and D) for bumetanide (A and B), and scopolamine (C and D) at their HIGH concentrations. Following the procedure of forced degradation, a decrease of each main peak was observed in different conditions tested (acidic, basic, oxidative, heating). Some degradation products are detectable on chromatograms and were not interfering with main peaks of bumetanide and scopolamine.

CHEMICAL STABILITY

After 18 days, the relative concentration of bumetanide at LOW and HIGH concentrations was unchanged: 100.1% of the initial content (C_0) with lower limits of the 95% confidence intervals on the means (LL95CI) of 99.6% for the LOW concentration and 100.3% of C_0 with a LL95CI of 99.8% for the HIGH concentration.

Evolution of scopolamine concentration remained stable after 18 days with 99.2% (LL95CI of 99.0%) and 99.4% (LL95CI of 98.9%) of C_0 at LOW and HIGH concentrations, respectively.

FIGURE 2 shows the degradation rates according to the different molecules and the different concentrations. The bumetanide content did not decrease through the 18 days of test with a mean slope of $3.48e^{-5}$ per day [LL95CI: $-3.82e^{-4}$] and $1.86e^{-4}$ per day [LL95CI: $-2.31e^{-4}$] for LOW and HIGH concentrations, respectively. Degradation rates of bumetanide content at LOW and HIGH concentrations should not exceed 0.38% and 0.23% every 10 days. The scopolamine content remained stable through the 18 days of test at LOW concentration (slope of $-3.60e^{-4}$ with LL95CI $-6.61e^{-4}$) and at HIGH concentration (slope of $-3.99e^{-4}$ with LL95CI $-7.00e^{-4}$). Degradation rates of scopolamine content at LOW and HIGH concentrations should not exceed 0.66% and 0.70% every 10 days.

Discussion

In palliative-care units, comfort and safety are of the greatest importance for patients and relatives. In order to limit fluid overload in end-stage of life patients, administration of bumetanide, a loop diuretic, could be added to scopolamine treatment through previously prepared polypropylene syringes. The co-infusion of bumetanide and scopolamine presents numerous advantages, notably the preparation in advance under aseptic condition by a CIVAS in-hospital pharmacy department, resulting in decreased workload and preparation errors.[11]

The 6th edition of the Palliative Care Formulary does not mention any compatibility of the binary mixture bumetanide and scopolamine,[16] and the "Stabilité des medicaments en perfusion" database, released in January 2021, does not report any information about this admixture.[8,10] A UHPLC method was specifically developed and validated, and the forced-degradation study proved that the method was stability indicating.

This study is the first one to evaluate the stability of the admixture of bumetanide and scopolamine at different concentrations usually used in palliative-care units. Our results show that polypropylene syringes containing bumetanide and scopolamine at two different concentrations (bumetanide: 41.67 µg/mL and scopolamine: 5.21 µg/mL for lowest concentration and bumetanide: 125 µg/mL and scopolamine: 31.25 µg/mL for highest concentration) are physically and chemically stable for 18 days at 5°C ± 3°C since their concentrations remain higher than the threshold of 90% required to deem the product chemically stable following the ICH rules.

Our study presents some limitations such as the lack of microbiological stability studies. However, the pharmaceutical preparation can be assimilated to low-risk compounding based on criteria (e.g., the process simplicity and the aseptic environment of production).[17] Other limitations are the absence of stability studies performed at room temperature and the limited time of follow-up.

Conclusion

The combination of bumetanide and scopolamine for IV drug solution is stable and compatible with a ready-to-use preparation made in advance under aseptic condition by a CIVAS in the Department of Pharmacy.[18]

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