Long-term Physicochemical Stability of Concentrated Solutions of Salbutamol (Albuterol) in Polypropylene Syringes for Use in the Intensive Care Unit and in Obstetrics

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Abstract

In order to avoid fluid overload, the use of more concentrated drug solutions in intensive care units and obstetrics is common. The objective of this study was to quantify the physicochemical stability of a concentrated solution of salbutamol (albuterol) in polypropylene syringes during 30 days of storage at 5°C ± 3°C with protection from light. Four 50-mL syringes containing 0.060 mg/mL of salbutamol (albuterol) in 0.9% NaCl were prepared and stored at 5°C ± 3°C with protection from light during 30 days of storage. Immediately after preparation and periodically during the storage, salbutamol (albuterol) concentrations were measured by an ultra-performance liquid chromatography. Spectrophotometric absorbance at different wavelengths, pH measurement, and microscopic observations were also performed. All solutions were physicochemically stable during the entire period storage at 5°C ± 3°C: no color change, turbidity, precipitation or opacity, significant pH variations, or optic densities were observed in the solutions. No crystals were seen by microscopic analysis. Concentrations of salbutamol remained stable during the storage period. Solutions of salbutamol (albuterol) 0.060 mg/mL in syringes of 0.9% NaCl are physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C with protection from light and may be prepared in advance by a centralized intravenous additive service.

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Introduction

Salbutamol sulfate (albuterol sulfate) is a short-acting, β2-adrenergic receptor agonist indicated for the relief of severe broncho-spasm in conditions such as asthma and chronic obstructive pulmonary disease.[1-2] Moreover, it can be used in obstetrics in pregnant women who started their onset of labor between 22 weeks and 37 weeks of gestation in order to temporarily delay the fetal expulsion.[1] It can be administered by five different routes: 1) oral, 2) inhaled, 3) intravenous (IV), 4) subcutaneous, or 5) intramuscular. The total volume of infusion administered to patients admitted into intensive care units (ICUs) is often important. Fluid overload is commonly implicated in fluid resuscitation and is associated with increased hospital costs, morbidity, and mortality. Sometimes fluid overload can also induce other side effects such as hypernatremia. There is a huge interest to build strategies that reduce excessive fluid infusions.

In order to reduce the perfusion volume and prevent fluid overload, the intensivists and the obstetricians may prefer to administer a higher salbutamol (albuterol) IV concentration using an injection syringe.[3-6]

The chemical and physical in-use stability of salbutamol at 0.01 mg/mL stored for 24 hours at 20°C to 25°C in 5% dextrose and 0.9% NaCl solutions was discussed by Trissel.[7] In 2017, Closset et al conducted a physical study of highly concentrated injectable drug solutions with a 48-hour storage period, which were used in intensive care units,[8] but the chemical stability of the highly concentrated injectable solutions remains unknown.

The objective of this study was to determine the physical and chemical stability of a higher concentration of salbutamol (0.060 mg/mL) diluted in 0.9% NaCl in polypropylene syringes.

Materials and Methods

SOLUTION PREPARATION

Four 50-mL polypropylene syringes (Lot 1702229P, Per: 01/2022; Becton Dickinson, Erenbodegem, Belgium), containing 0.060 mg/mL of salbutamol (albuterol) (Lot 6501, Per: 05/2019; GSK, Wavre, Belgium) in 0.9% NaCl (Lot 165048131, Per: 11/2019; B Braun, Diegem, Belgium) were prepared under laminar airflow and stored at 5°C ± 3°C for 30 days with protection from light.

Standard and Quality-control Solutions

A 1-mg/mL standard solution of salbutamol (Salbutamol Ventolin) (Lot 6501, Per: 05/2019; GSK) was diluted in purified water to obtain five standard solutions (0.125 mg/mL, 0.090 mg/mL, 0.062 mg/mL, 0.031 mg/mL, and 0.016 mg/mL) and two quality controls (0.060 mg/mL and 0.030 mg/mL).

Chromatographic Conditions

The chromatography was performed on a Waters Acquity ultra-performance liquid chromatography (UPLC) H-Class system (Waters Association, Milford, Massachusetts) with a photodiode array detector (PDA) (Acquity UPLC PDA; Waters Association) and a data acquisition and processing module (Empower 2 Software; Waters Association). Separation was performed on a reversed-phase column (Lot 0141370301, Waters Acquity UPLC CSH C18, 1.7 µm, 2.1×100 mm; Waters Association).

The mobile phase A was constituted of 10% acetonitrile (Lot 1123601, Per: 07/2019, ULC/MS grade acetonitrile; Biosolve BV, Valkenswaard, The Netherlands) and 90% KH_2PO_4 buffer (pH 4.65; 0.025M) (Ref 1.04873.1000, KH_2PO_4; Merck, Darmstadt, Germany) and H_3PO_4 (Ref 10G090501; VWR International, Fontenay-sous-Bois, France). This UPLC-grade solvent was then filtered through a 0.20-µm membrane filter (Lot R2BA85869; Durapore). The mobile phase B was constituted of 100% acetonitrile (Lot 1123601, Per: 07/2019; Biosolve BV).

The step-gradient program is described in TABLE 1.

The flow rate was set at 0.15 mL/min, the column temperature at 35°C, and the wavelength (PDA detector) at 210 nm.

PHYSICAL STABILITY

Physical compatibility was defined as the absence of particulate formation, haze, precipitation, color change, and gas evolution.[6] At each sampling interval, particle contamination was searched by visual and microscopic inspection and by optical density measurements. The samples were visually inspected with the unaided eye, in front of a black and white background, and the pellet obtained after centrifugation at 3000 rpm for 8 minutes was observed with a microscope 10 × (Carl Zeiss, Germany) for the detection of crystals. The optical densities were measured by a spectrophotometer (Genesys 10 UV; Spectronic Unican) at 350 nm, 410 nm, and 550 nm to detect subvisible particles.[9]

The pH of the solutions were measured with a pH-meter (Inolab WTW, Weilhein, Germany) equipped with a glass electrode (Biotrode Hamilton Bonaduz, Switzerland) calibrated with two standard solutions at pH 4 and pH 7 (CertiPur, Merck).

ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHIC ASSAY

Five standard solutions of 2 µL each were both checked for quality and samples were injected into the chromatograph. Results were automatically calculated by interpolation of a five-level calibration curve (linear through zero), performed by the Empower 2 software (Waters Association) using areas under salbutamol peak versus standard concentrations.

TABLE 1.

GRADIENT PROGRAM FOR THE ULTRA-HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD.

	TIME (MIN)	FLOW (ML/MIN)	M.P. A (%)	M.P. B (%)
1	Initial	0.150	100	0
2	4.00	0.150	88	12
3	5.00	0.150	85	15
4	6.00	0.150	60	40
5	8.00	0.150	100	0
6	9.00	0.150	100	0

Note: The percentages of mobile phase A (M.P. A) and mobile phase B (M.P. B) vary as a function of time.

VALIDATION OF THE METHOD

The within and between-day relative standard deviation (SD) values (n=10) were realized on two concentrations (0.030 mg/mL and 0.060 mg/mL). The determination coefficient r^2 was determined by a linear-regression analysis of peak area. Degraded samples of salbutamol solutions were assayed to confirm separation of the parent drug from its degradation products. Salbutamol solutions at natural, alkaline, and acidic pH were heated at 100°C during 15 minutes, 30 minutes, 45 minutes, and 60 minutes.

STABILITY STUDY

After preparation, the syringes were stored for 30 days at 5°C ± 3°C. The concentrations of salbutamol were determined in triplicate for each of the syringes immediately after preparation and every day for the first 4 days then every 2 working days until the 30th day.

STATISTICAL ANALYSIS

As recommended by the U.S. Food and Drug Administration, solutions are considered stable if the lower limit of the 9% one-sided confidence interval of the mean remains superior to 90% of the initial concentration[10] or 95% of the initial concentration when any signs of physical instability exist.[11] Chemical stability of salbutamol was confirmed with the use of prediction interval in lieu of confidence interval.

Results

VALIDATION OF THE METHOD

The within and between-day relative SD values are shown in TABLE 2 and could be considered as acceptable. The linearity of the assay can be validated from 0.016 mg/mL to 0.125 mg/mL (determination coefficient r^2 >0.997). No additional peak from decomposition products has been reported (FIGURE 1).

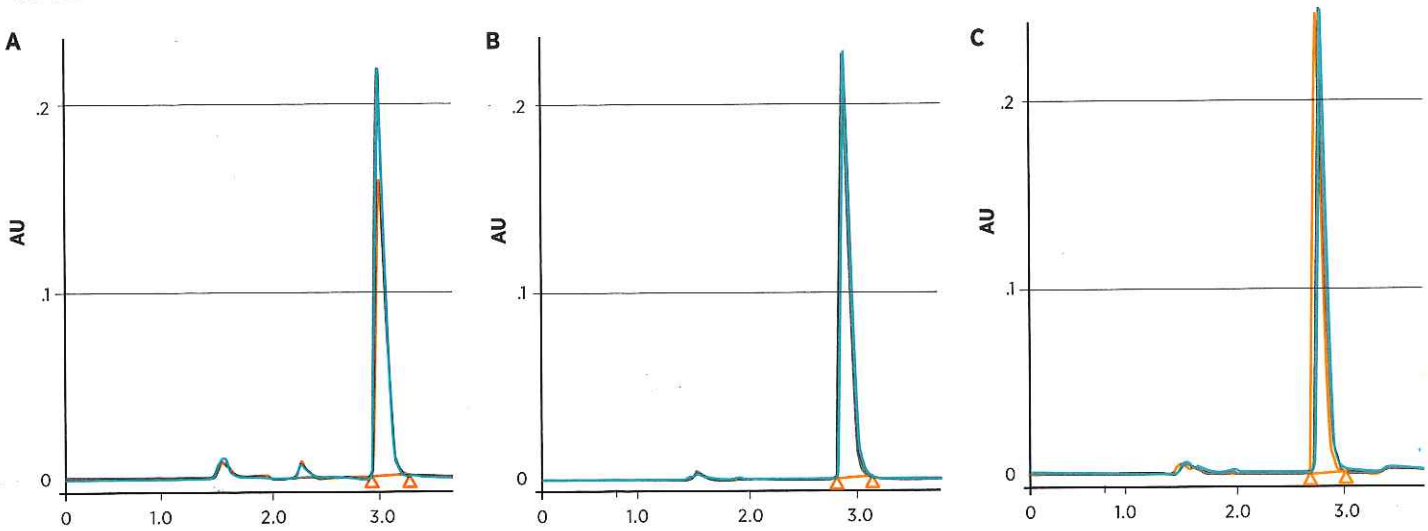
TABLE 2.

INTRA-REPRODUCIBILITY AND INTER-REPRODUCIBILITY OF THE ASSAY.

CONCENTRATIONS	WITHIN-DAY CV (%) ± STANDARD DEVIATION (*n*=10)	BETWEEN-DAY CV (%) ± STANDARD DEVIATION (*n*=10)
0.03 mg/ mL	1.1 ± 0.3	2.0 ± 0.7
0.06 mg/ mL	1.4 ± 0.8	1.9 ± 1.2

FIGURE 1.

DEGRADATION CHROMATOGRAMS.



Note: (A) = degradation at alkaline pH; (B) = degradation at natural pH; and (C) = degradation at acidic pH. The chromatograms are superimposable for the different times of degradation.

PHYSICAL STABILITY

All solutions were physically stable during the entire storage period: no color change, turbidity, precipitation or opacity, significant variation in pH values (mean ± SD: 5.448 ± 0.436; minimum – 4.939; maximum – 6.430), or optical densities were observed in the solutions. No crystals were seen by microscopic analysis.

CHEMICAL STABILITY

The salbutamol content remained stable throughout the study (FIGURE 1 and TABLE 3). These data support a chemical stability for at least 30 days. Any additional chromatographic peak did not appear over the entire study period.

Discussion

IV salbutamol infusions are commonly used in the ICUs and emergency medicine to treat severe bronchospasm and are also used in obstetrics to temporarily delay the fetal expulsion.[1] In the ICU, special attention is paid to the fluid balance of the patients, especially the total volume of infusion and the prevention of fluid overload.[3,4,6] The management of fluid balance when infusing, as well as the possible adverse effects of fluid overload, remains a frequent concern and discussion of many disease states. Reducing the global volume of infusion by using a more concentrated drug solution is a possible way to manage fluid overload.[4]

Similarly, the product monograph recommends the reduction of the global volume of infusion to avoid risk of pulmonary edema in the pregnant mother. Indeed, parenteral forms are nowadays more often used in obstetrics, as the European Medicine Agency recommended to no longer use the oral and suppositories formulations in any obstetric indication.[12]

Data are lacking about the stability of concentrated solutions of salbutamol in syringes. The product monograph only mentions that in-use storage times would normally not be longer than 24 hours at 2°C to 8°C.[1] Maithani and Singh[2] described a degradation of salbutamol in tablet form for 24 hours. Salbutamol sulfate was labile to acid and alkaline hydrolysis but stable in neutral condi-

TABLE 3.

EVOLUTION OF THE RELATIVE CONCENTRATION OF SALBUTAMOL FROM DAY 0 TO DAY 30.

DAY	MEAN	SD	LL 95 CI	LL 95 PI
0	99.4	2.0	99.5	97.4
1	99.7	1.7	99.5	97.4
2	99.2	1.6	99.5	97.4
3	100.1	2.1	99.5	97.4
4	101.0	1.5	99.5	97.4
7	100.2	2.1	99.5	97.3
9	100.4	1.2	99.5	97.3
11	99.6	1.8	99.5	97.3
14	99.7	1.6	99.4	97.2
16	100.2	1.7	99.4	97.2
18	99.5	0.9	99.3	97.1
21	99.4	1.1	99.2	97.1
23	98.9	2.1	99.1	97.0
25	100.0	1.1	99.0	97.0
28	98.9	1.1	98.9	96.9
30	99.7	1.1	98.8	96.8

Initial concentration: 62.2 g/100 mL ± 0.93 g/100 mL
LL 95 CI = lower limit of the 95% confidence interval on the mean; LL 95 PI = lower limit of the 95% prediction interval; SD = standard deviation

tions. Profound degradation was also seen with thermal stress. Nevertheless, the syringes were protected from light throughout the study to avoid any effect on stability.

Our results show that solutions of salbutamol 0.060 mg/mL in 0.9% NaCl were physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C with protection of light.

Only the physical and chemical stabilities were evaluted, and the microbiological aspects were not investigated. However, according to Chapter <797> of the *United States Pharmacopeia*, our preparation can be assimilated to low-risk compounding.[13]

These results allow us to add this solution to the list of our systematic studies of the chemical stability of ready-to-use, long-term IV drug solutions,[14] and the advanced preparation by a centralized intravenous additive service (CIVAS) may be considered.[15]

Conclusion

Solutions of salbutamol 0.060 mg/mL in 0.9% NaCl are physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C with protection from light and may be prepared in advance by a CIVAS. This concentration may be particularly useful in the ICU to treat patients and prevent fluid overload.

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