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Stability of intravenous amiodarone dilutions in 5% glucose from two commercial formulations

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Abstract

Aim of the study. This study aimed to assess the stability of amiodarone in two commercially available formulations, Amiokordin and Cordarone, at concentrations of 0.6 mg/mL and 4.4 mg/mL in 5% w/v glucose, stored at room temperature (22°C) and under refrigeration (6°C) for up to 48 hours, focusing on dilutions used in neonatal and infant administration. ***Material and methods.*** Amiodarone concentrations were measured using ultra-high-performance liquid chromatography with diode-array detection. Calibration curves were linear over the range of 0.1–7.5 mg/mL. Stability was defined as retention of 90–110% of the initial concentration. Results were expressed as percent deviation from the initial (0 h) concentration, where 0% corresponds to the initial value (100%). ***Results.*** For Amiokordin, mean relative accuracy ranged from −5.9±1.8% to 5.8±2.9%. For Cordarone, these values ranged from 2.8±3.6% to 10.4±3.4%; however, some individual results exceeded ±10% but remained within ±15%. ***Conclusion.*** Amiodarone at 0.6 and 4.4 mg/mL remained stable in both formulations for up to 48 hours under the tested conditions, except for the borderline stability of Cordarone stored at 6°C for 48 hours. These results support short-term preparation and storage in neonatal practice. However, because the UHPLC method was not validated as stability-indicating, the presence of potential degradation products cannot be excluded. *(Farm Współ 2026; 19: 79-87) doi: 10.53139/FW.20261915*

Keywords: amiodarone, neonatology, drug stability, intravenous administration, pharmacy service, pharmacists

Introduction

Amiodarone is used to treat life-threatening ventricular arrhythmias, such as ventricular fibrillation or pulseless ventricular tachycardia, in children with cardiac arrest [1,2]. In infants (≤1 year of age), it is also used to prevent recurrence of prolonged supraventricular tachycardia and its potential hemodynamic consequences [3]. The adverse effects observed in children are similar to those reported in adults and include hypotension, thyroid dysfunction, QTc prolongation, hepatic dysfunction, and, in severe cases, cardiovascular collapse or death [2,4,5].

In newborns and infants, amiodarone is administered exclusively in hospital settings, most often in neonatal or cardiac intensive care units, under close monitoring (electrocardiography, blood pressure, oxygen saturation, and thyroid and liver function tests). Amiodarone has a very long and variable elimination half-life (30–100 days) [6]. Therefore, precise dosing is essential, particularly in neonates and preterm infants. According to NeoFax [7], which is an evidence-based drug reference and dosing database specifically designed for neonates and infants, amiodarone is the most frequently administered at a dose of 5-10 mg/kg with a maximum of 20 mg/kg (loading dose of 5 mg/kg, maintenance infusion 10-20 mg/kg per 24 hours).

In Poland, available intravenous amiodarone formulations include Amiokordin (Krka, Novo mesto, Slovenia) and Cordarone (Sanofi Winthrop Industrie, Gentilly, France), both supplied in 3 mL ampoules at

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a concentration of 50 mg/mL. Data on the stability of clinically relevant amiodarone dilutions in 5% glucose remain limited and inconsistent. Because amiodarone is incompatible with 0.9% sodium chloride solution, it is recommended that it be administered undiluted or diluted only in 5% glucose [8,9]; however, information on the stability of dilutions is scarce. Available studies report variable stability depending on concentration, storage conditions, and container materials [8–14], with particular concern regarding sorption to polyvinyl chloride infusion systems [15]. These gaps are especially relevant in clinical practice, including neonatal intensive care units, where individualized dosing requires preparing low-concentration amiodarone solutions.

Although there is a clear clinical and practical need, published information on the stability of amiodarone in Amiokordin and Cordarone formulations at concentrations below 50 mg/mL remains limited, particularly for preparations stored for extended periods at different temperatures. Evaluating the stability of these lower-strength solutions is crucial to ensure dosing accuracy and safety, minimizing the risk of degradation, and supporting reliable compounding practices in hospital pharmacy settings. Therefore, this study aimed to evaluate the stability of amiodarone solutions at concentrations of 0.6 mg/mL and 4.4 mg/mL in 5% glucose, stored at room temperature and under refrigeration for 24 and 48 hours.

Materials and Methods

Chemicals and reagents

Amiodarone was obtained as Amiokordin (Krka, Novo mesto, Slovenia) and Cordarone (Sanofi Winthrop Industrie, Gentilly, France), both supplied in 3 mL ampoules at a concentration of 50 mg/mL. These solutions were used as reference standards for calibration and validation. The 5% w/v glucose solution was manufactured by Fresenius Kabi Polska Sp. z o.o. (Warsaw, Poland). Acetic acid and ammonium hydroxide for preparation of the mobile phase were purchased from Chempur (Piekary Śląskie, Poland) and J. T. Baker (Spain), respectively. Acetonitrile (LC grade) was obtained from Merck (Darmstadt, Germany).

Chromatographic conditions

The chromatographic method was adapted from the literature [16]. The analysis was performed using a Shimadzu ultra-high-performance liquid chromatography (UHPLC) system (Shimadzu Co., Kyoto, Japan), equipped with a solvent degasser (DGU-20A5), binary pump (LC-20AD), thermostated autosampler (SIL-30AC), and column oven (CTO-20AC). Detection was performed using a diode array detector (DAD) at 240 nm. Data were processed using LabSolutions software (Shimadzu, Kyoto, Japan). A Zorbax Eclipse Plus C18 analytical column (2.1 mm × 100 mm, 3.5 µm, Agilent, USA) was used. The mobile phase consisted of 50 mM acetate buffer pH 5.5 (A) and acetonitrile (B) mixed at a ratio of 10:90 (v/v). The injection volume was 5 µL, and the flow rate was 0.6 mL/min. The retention time of amiodarone was approximately 4.2 minutes for both formulations.

Working solutions

Amiokordin and Cordarone (50 mg/mL) were used as stock solutions. On each day of analysis, working solutions were freshly prepared in 5% w/v glucose at concentrations: 0.1, 0.25, 0.5, 1, 2.5, 5, and 7.5 mg/mL. Before injection, samples were diluted 10-fold with the mobile phase (10 µL of working solution mixed with 90 µL of mobile phase), vortex-mixed, and injected into the UHPLC system. Calibration curves were prepared separately for Amiokordin and Cordarone. No internal standard was used because only infusion solutions (not biological matrices) were analyzed, and no extraction procedures were required. Within-run accuracy and precision were evaluated using quintuplicate measurements (n=5), and between-run accuracy and precision were assessed in triplicate (n=3). A t-test was used to determine whether the intercept differed significantly from zero, with statistical significance set at $p < 0.05$.

Stability assessment

For stability testing, amiodarone solutions were prepared at concentrations of 0.6 mg/mL and 4.4 mg/mL in 5% w/v glucose and stored for 48 hours at room temperature (22°C) and under refrigeration (6°C), reflecting typical hospital pharmacy and ward conditions. Samples were stored in capped polypropylene tubes, protected from light, and analyzed at 24 and 48 hours. Visual inspection was performed to assess the presence of precipitation, turbidity, or discoloration.

Calculations

For quality control (QC) samples, precision was expressed as the coefficient of variation (CV, %): $CV = (SD/C_{back\text{-}calculated}) \times 100\%$. Accuracy was calculated as: $Accuracy\ (\%) = (C_{back\text{-}calculated}/C_{nominal}) \times 100\%$.

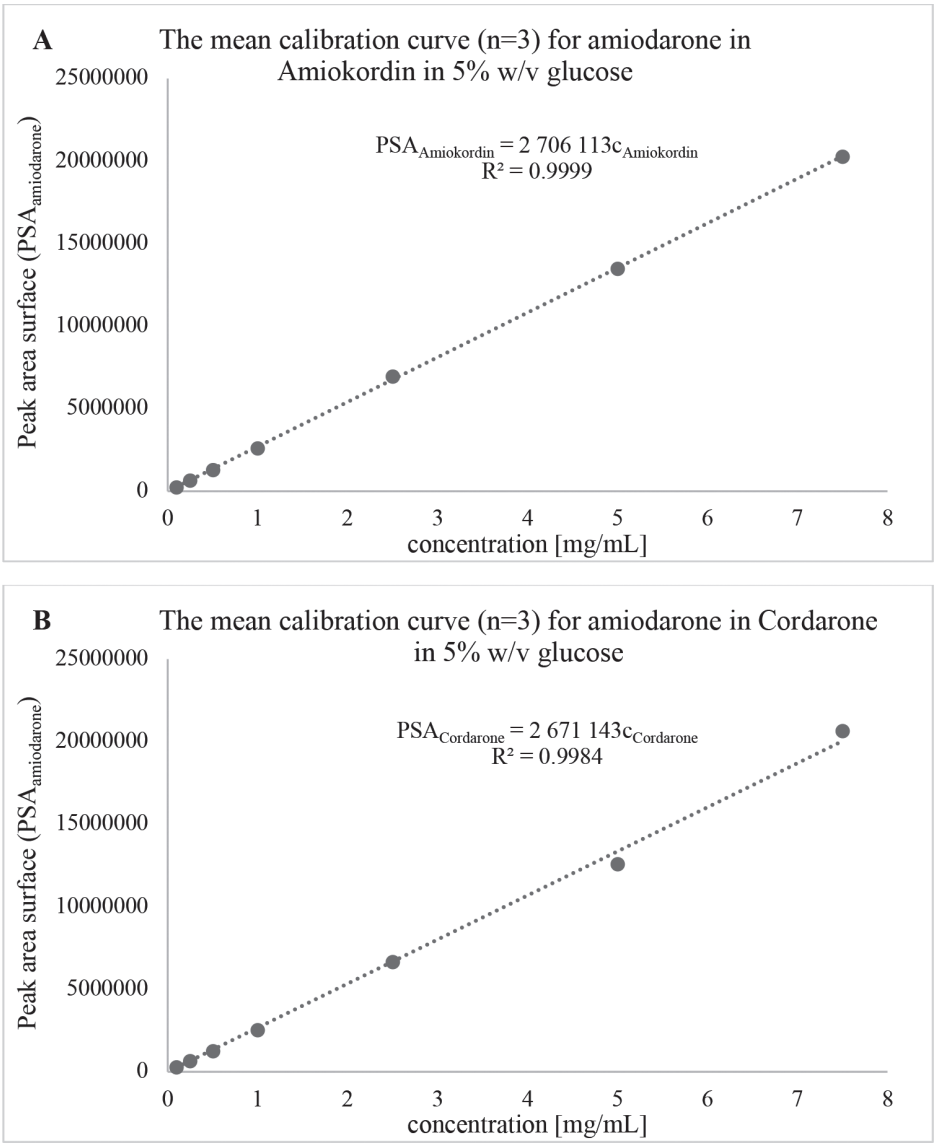
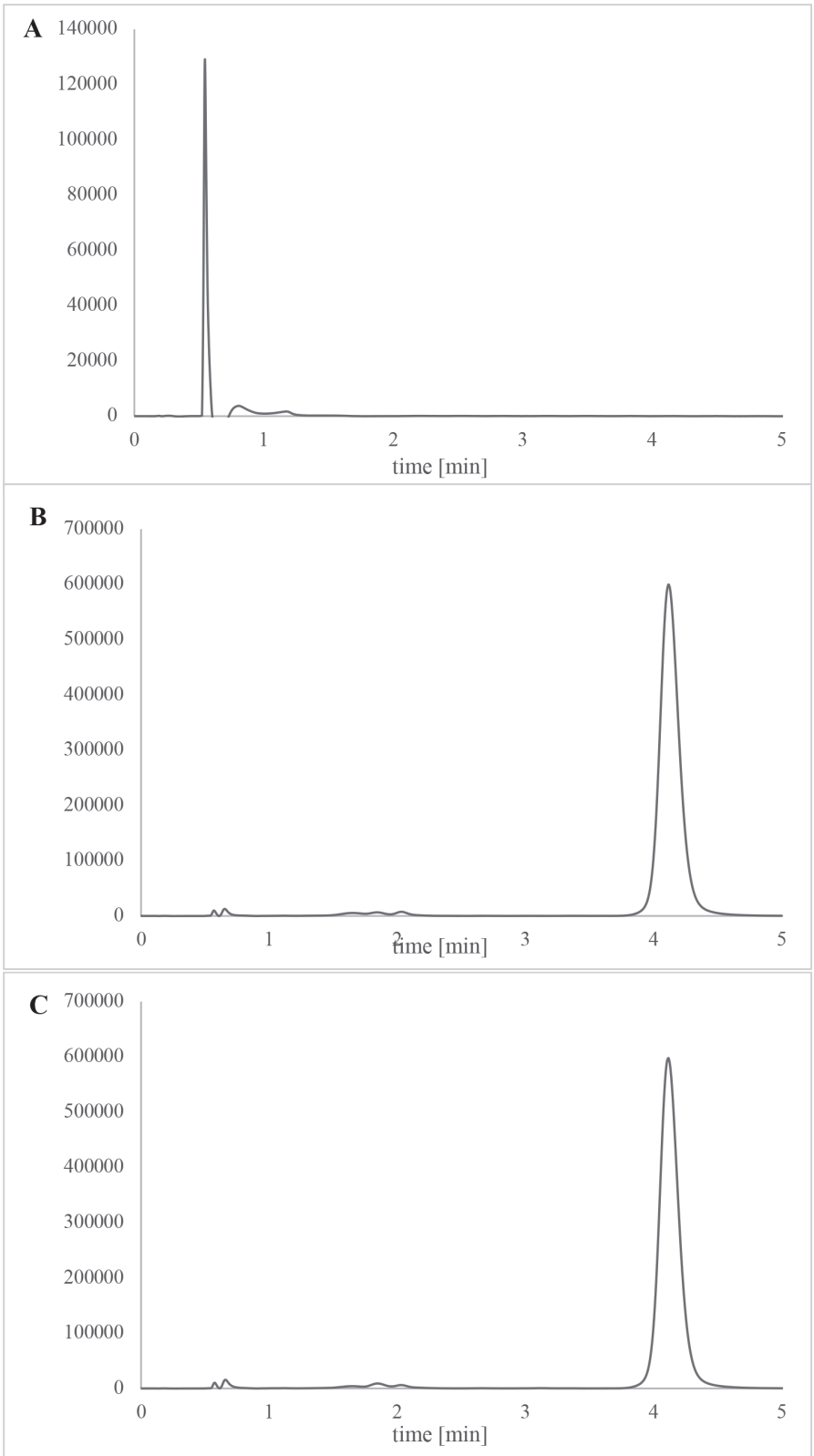


Figure 1. Calibration curves, including the regression equations and correlation coefficients, for amiodarone from (A) the Amiokordin formulation and (B) the Cordarone formulation, both diluted in 5% w/v glucose

Stability was assessed based on the retention of amiodarone concentration over time. Test samples were divided into at least three aliquots, stored, and analyzed against a calibration curve prepared from fresh standards. A preparation was considered chemically stable if the measured concentration remained within 90–110% of the initial value (time 0), in line with pharmacopeial recommendations for compounded preparations (e.g., USP) [17]. Stability was expressed as relative accuracy (%) with respect to the initial (0-hour) concentration, where 0% corresponds to 100% of the initial concentration. In addition, the variability of analytical measurements was interpreted with reference to the commonly accepted bioanalytical validation criteria (±15%), to distinguish potential analytical variability from physicochemical instability [18].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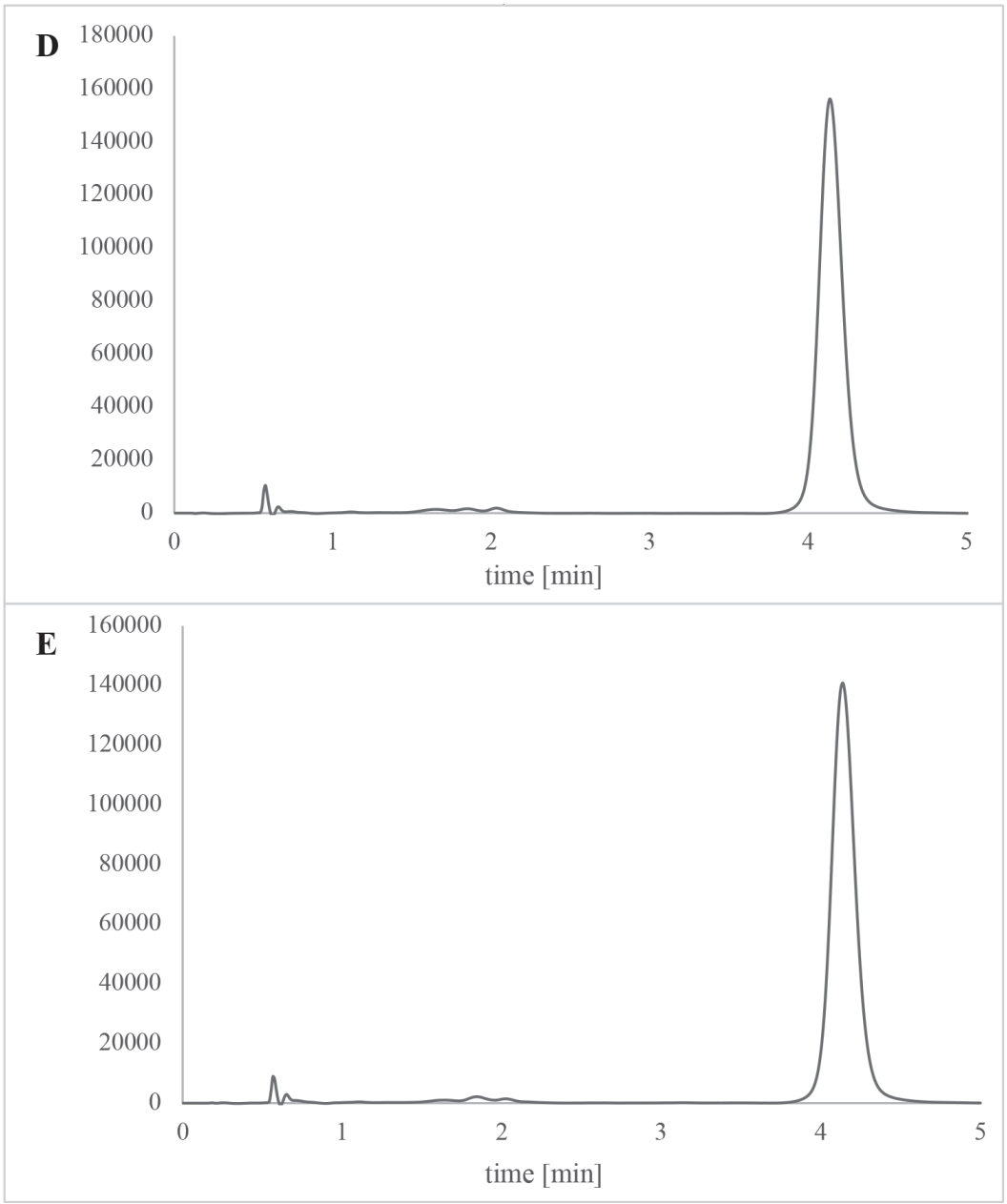

Figure 2. The representative chromatograms of (A) 5.0% w/v glucose (blank sample), (B) 5.0% w/v glucose spiked with amiodarone from Amiokordin formulation (2.5 mg/mL), (C) 5.0% w/v glucose spiked with amiodarone from Cordarone formulation (2.5 mg/mL), (D) amiodarone (0.6 mg/mL) from Amiokordin formulation in 5% w/v glucose stored at refrigerator for 24 hours, (E) amiodarone (0.6 mg/mL) from Cordarone formulation in 5% w/v glucose stored at room temperature for 24 hours

Table I. Intra-day and inter-day precision and accuracy for the determination of amiodarone in Amiokordin and Cordarone in 5% w/v glucose

QC concentration	Precision (CV, %)		ICH acceptance criteria	Accuracy (%)		ICH acceptance criteria
	within--run	between--run		within--run	between--run	
	n=5	n=3		n=5	n=3	
Amiokordin						
0.1 mg/mL	4.6	9.8	< 20%	105.1	94.4	80-120%
0.25 mg/mL	7.6	8.8	< 15%	102.9	97.7	85-115%
2.5 mg/mL	3.5	6.1	< 15%	108.0	103.0	85-115%
7.5 mg/mL	1.9	4.4	< 15%	97.4	99.9	85-115%
Cordarone						
0.1 mg/mL	3.3	5.3	< 20%	91.2	90.9	80-120%
0.25 mg/mL	1.5	4.0	< 15%	91.7	93.8	85-115%
2.5 mg/mL	4.5	5.9	< 15%	102.6	99.5	85-115%
7.5 mg/mL	4.6	3.5	< 15%	103.3	102.9	85-115%

CV coefficient of variation; ICH, International Council for Harmonisation; QC quality control

The assay was not formally validated as stability--indicating, as no forced degradation studies (acidic, alkaline, oxidative, or thermal stress conditions) were performed to identify potential degradants.

Results

The calibration curves for amiodarone in 5% w/v glucose were linear over the range of 0.1-7.5 mg/mL for both formulations. The mean calibration equations (n=3) were:

$$PSA_{Amiokordin} = 2706113 \cdot C_{Amiokordin}$$ for Amiokordin,

$$PSA_{Cordarone} = 2671143 \cdot C_{Cordarone}$$ for Cordarone,

where PSA denotes the peak surface area, and C represents the amiodarone concentration for each formulation. The coefficients of determination (R^2) were 0.9999 for Amiokordin and 0.9984 for Cordarone. As the intercepts were negligible and not statistically different from zero ($p > 0.05$), calibration curves were forced through zero. Full calibration equations and representative chromatograms are provided in figu-

Table II. The stability of Amiokordin in 5% w/v glucose, expressed as relative accuracy (%) with respect to the initial (0 h) concentration

Nominal concentration	Room temperature (22°C)		Refrigerator (6°C)	
	24 h	48 h	24 h	48 h
0.6 mg/mL	-5.8	1.9	8.0	-1.5
	-4.1	2.8	3.9	2.3
	-7.7	4.2	-3.5	6.9
mean ± SD	-5.9 ± 1.8	3.0 ± 1.1	2.8 ± 5.8	2.5 ± 4.2
4.4 mg/mL	-3.3	0.9	5.2	1.8
	2.3	5.9	3.3	5.0
	-2.0	6.9	9.0	9.9
mean ± SD	-1.0 ± 2.9	4.5 ± 3.2	5.8 ± 2.9	5.6 ± 4.1

Data expressed as percentages of the nominal concentration, SD, standard deviation

Table III. The stability of Cordarone in 5% w/v glucose, expressed as relative accuracy (%) with respect to the initial (0 h) concentration

Nominal concentration	Room temperature (22°C)		Refrigerator (6°C)	
	24 h	48 h	24 h	48 h
0.6 mg/mL	-1.3	9.3	6.1	9.7
	12.0	7.6	3.4	14.1
	-0.4	5.9	-1.1	7.5
mean ± SD	3.5 ± 7.4	7.6 ± 1.7	2.8 ± 3.6	10.4 ± 3.4
4.4 mg/mL	11.3	9.1	-3.2	8.6
	6.8	10.7	12.6	10.1
	7.7	9.1	6.3	7.4
mean ± SD	8.6 ± 2.3	9.6 ± 0.9	5.2 ± 8.0	8.7 ± 1.4

Data expressed as percentages of the nominal concentration, SD, standard deviation

res 1 and 2, respectively. The method demonstrated acceptable within-run (n=5) and between-run (n=3) accuracy and precision for both formulations (table I).

The stability results for amiodarone in Amiokordin and Cordarone, diluted in 5% w/v glucose, are presented in tables II and III, respectively. For both formulations and both tested concentrations (0.6 mg/mL and 4.4 mg/mL), the mean relative accuracy remained within ±15% of the initial concentration under all tested conditions, indicating no major loss of drug content.

Discussion

This study aimed to evaluate the short-term stability (up to 48 hours) of amiodarone at two clinically relevant concentrations (0.6 and 4.4 mg/mL) in Amiokordin and Cordarone formulations prepared for neonatal use. To our knowledge, stability data for these specific dilutions in routine clinical practice have not been reported previously, despite their frequent preparation in neonatal intensive care settings, where individualized dosing is required for extremely low-birth-weight infants. In the Department of Neonatology at Poznan University of Medical Sciences, the amiodarone concentrations of 0.6 and 4.4 mg/mL are the most frequently used.

Published data on amiodarone stability in 5% glucose (dextrose) solutions remain limited and heterogeneous. Although amiodarone is considered incompatible with 0.9% sodium chloride solution [8,9], some studies have reported short-term stability in this medium under selected conditions [9]. According to the Summaries of Product Characteristics, amiodarone should be administered undiluted or diluted exclusively in 5% w/v glucose solution. However, while concentrations below 0.6 mg/mL (i.e., 300 mg in 500 mL of 5% glucose solution) are described as unstable, the duration of stability for higher concentrations is not clearly specified.

Available literature indicates that stability strongly depends on concentration, storage conditions, and container material. According to the South Eastern Sydney Local Health District guideline, amiodarone solutions at concentrations of 600 µg/mL to 6 mg/mL in 5% glucose are stable for 24 h at 25°C, whereas concentrations above 6 mg/mL are stable for only 12 h [10]. Lardinois et al. [11] demonstrated physicochemical stability of amiodarone 25 mg/mL in 5% dextrose stored in polypropylene syringes for 28 days at 5°C with light protection. Pramar [8] reported stability at lower concentration in both 5% dextrose and 0.9% sodium chloride. Similarly, Hecq et al. [14] and Closset et al. [13] confirmed short-term physical stability (48 hours) of highly concentrated preparations (50 mg/mL and 25 mg/mL, respectively) in polypropylene syringes at room temperature. Berthouzoz et al. [12] reported long-term refrigerated stability of centralized ready-to-use preparations (12.5 mg/mL). In contrast, Yang et al. [9] showed that amiodarone at 1 mg/mL remained stable for 8 hours at room temperature without light protection in several commonly used infusion

fluids (0.9% sodium chloride injection, sodium lactate Ringer's injection, glucose sodium chloride injection; 5% and 10% glucose injections). According to NeoFax [7], amiodarone suspension at a concentration of 5 mg/mL in plastic bottles is stable for at least 42 days at 25°C and 91 days at 4°C.

Earlier studies also highlighted the potential for sorption of amiodarone to polyvinyl chloride (PVC) infusion systems. Weir et al. [15] demonstrated significant drug loss during prolonged storage (120 hours), particularly in PVC containers, suggesting that plastic materials (e.g., di-2-ethylhexyl phthalate) may influence the apparent stability of diluted solutions. Visual incompatibility was also observed after 24 hours of storage in glass containers.

In the present study, both concentrations (0.6 and 4.4 mg/mL) in the Amiokordin formulation remained stable for 48 hours at 6°C and 22°C according to pharmacopeial acceptance criteria (90–110%). For Cordarone, all storage conditions met the predefined acceptance criterion except for the 0.6 mg/mL solution stored at 6°C for 48 h, for which the mean relative accuracy was 10.4%. Although this value exceeded the predefined pharmacopeial limit by only 0.4%, this condition should be regarded as borderline and interpreted with caution.

This study has several limitations. First, only two concentrations and two storage temperatures were evaluated. Higher temperatures, such as those encountered in neonatal incubators, may also be clinically relevant. Second, although a validated UHPLC method was used, the assay was not formally demonstrated to be stability-indicating, as forced degradation studies were not performed. Therefore, while the results suggest preservation of drug content, the presence of potential degradation products cannot be excluded. Third, microbiological stability was not assessed because the solutions were assumed to have been prepared under aseptic hospital pharmacy conditions. Finally, additional physicochemical parameters, such as pH, osmolality, visible and subvisible particulate matter, were not evaluated. Since the study focused on the chemical stability of commercially available formulations after dilution in 5% glucose, only drug concentration and visual appearance were assessed. These complementary aspects may further support physicochemical stability and should be addressed in future studies, particularly for neonatal applications. Although a 10% degradation threshold is widely used in the literature, it is not universally applicable and should be interpreted in the context of the drug, formulation, and potential degradation products. Methodological guidance for hospital pharmaceutical preparations also indicates that concentration changes alone may not fully reflect stability, and additional physicochemical factors should be considered [19,20].

From a practical perspective, the demonstrated 48-hour stability of amiodarone may facilitate centralized preparation of amiodarone dilutions in hospital pharmacies. It could reduce the preparation workload on clinical wards, minimize drug wastage from unused preparations, and improve the availability of ready-to-administer doses for neonatal intensive care units.

Conclusion

Our findings support the short-term stability (48 h) of amiodarone at 0.6 and 4.4 mg/mL in both Amiokordin and Cordarone formulations stored under typical hospital pharmacy and ward conditions. The one exception is 0.6 mg/mL Cordarone dilution stored at 6°C for 48 h, which slightly exceeded the predefined pharmacopeial acceptance limit. These data may help support compounding practices in neonatal intensive care units. However, because the analytical method was not validated as stability-indicating, these results should be interpreted as evidence of concentration stability rather than confirmation of the absence of degradation products.

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Conflict of interest
Brak/None

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