

Article

Y-Site Compatibility of Doxapram Hydrochloride with Commonly Used Drugs in the NICU

Mao Maekawa ¹, Masamitsu Maekawa ^{1,*}, Yu Sato ², Shimpei Watanabe ³, Masatoshi Saito ³
and Nariyasu Mano ¹

¹ Department of Pharmaceutical Sciences, Tohoku University Hospital, Sendai 980-8574, Japan; mao.maekawa.d3@tohoku.ac.jp (M.M.); nariyasu.mano.c8@tohoku.ac.jp (N.M.)

² Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, Sendai 981-8558, Japan; sato.yu@tohoku-mpu.ac.jp

³ Center for Perinatal and Neonatal Medicine, Tohoku University Hospital, Sendai 980-8574, Japan; shimpei.watanabe.c2@tohoku.ac.jp (S.W.); masatoshi.saito.b4@tohoku.ac.jp (M.S.)

* Correspondence: masamitsu.maekawa.a2@tohoku.ac.jp

Abstract

In neonatal intensive care units (NICUs), limited vascular access often necessitates the co-administration of multiple intravenous medications through a single line, increasing the risk of physicochemical incompatibility. Doxapram hydrochloride (DOP), a respiratory stimulant used when caffeine therapy is insufficient, is continuously infused and frequently requires Y-site administration with other drugs. This study systematically evaluated the compatibility of seven commonly used NICU medications—midazolam (MDZ), dalteparin sodium (DLT), cefazolin, cefepime (CFPM), vancomycin, fosfluconazole, and famotidine—under conditions simulating co-administration through the side port of a continuous DOP infusion. Visual inspection, UV absorbance, pH measurement, and HPLC/UV analysis were performed at 0 and 3 h, with extended evaluation to 24 h for only MDZ and DLT. All mixtures showed acceptable physicochemical compatibility within 3 h, and MDZ and DLT remained stable for 24 h, indicating feasibility for co-infusion in the same syringe. In HPLC/UV analysis, the CFPM–DOP mixture exhibited a marked artifactual increase in DOP peak area, likely due to pH-dependent chromatographic behavior changing rather than true incompatibility. These findings provide practical compatibility data for NICU drug administration and offer a methodological framework for evaluating untested drug combinations, contributing to safer and more efficient intravenous therapy in preterm infants.

Keywords: neonatal intensive care units; stability; co-administration; compatibility; doxapram hydrochloride



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1. Introduction

In neonatal intensive care units (NICUs), various injections—primarily anti-infective agents, cardiovascular drugs, sedatives, and nutritional solutions [1]—are frequently administered. The methods of administration vary depending on the drug, including both intermittent and continuous infusions. In routine NICU practice, the number of required drug infusions sometimes exceeds the available intravenous (IV) lines. In such cases, clinicians must either secure an additional IV line—carrying risks such as mechanical injury, infection, and thrombosis—or administer multiple drugs through a single line via Y-site administration [2–5]. In Y-site administration, drugs are prepared separately and mix at the junction point before entering the bloodstream. However, when mixed within a catheter,

precipitation may occur because of physicochemical incompatibilities, and fatal embolic events have been reported following the injection of incompatible drugs [6,7].

Although compatibility among injectable drugs in the NICU has been reviewed using database-based analyses [2–5], the available information remains insufficient. Therefore, it is essential to verify the compatibility of untested drug combinations.

This study focused on doxapram hydrochloride (DOP), a respiratory stimulant continuously administered in the NICU when caffeine—the first-line treatment for apnea of prematurity—is ineffective [8–10]. Recent systematic reviews and clinical trials have highlighted both the potential benefits and the remaining uncertainties regarding DOP use in preterm infants. A Cochrane review including eight randomized controlled trials [8] ($n = 248$) reported that continuous intravenous infusion of DOP may slightly reduce the failure rate of apnea reduction compared with no treatment, although the certainty of evidence remains low. Another systematic review [9] showed that DOP decreased the frequency of apneic episodes compared with placebo, but its efficacy was comparable to that of methylxanthines such as theophylline. An earlier Cochrane review [10] also found no significant difference between intravenous DOP and methylxanthine therapy in reducing apnea within 48 h, with no major adverse effects reported. Meanwhile, an international multicenter randomized controlled trial (the DOXA trial) is ongoing to further clarify its safety and efficacy in extremely preterm infants (<29 weeks of gestation) [11]. Because of its short half-life, DOP requires continuous infusion [12], occupying one intravenous line. In preterm infants with limited vascular access, co-administration with other drugs is often necessary, making compatibility assessment clinically important.

A previous study evaluating the compatibility of DOP with 94 injectable drugs assessed parameters such as appearance, pH, osmolality ratio, and drug content [13]. Another study examined the physical compatibility of DOP with injectable medications commonly used in the NICU under simulated Y-site administration, where DOP was mixed with secondary drugs (e.g., antimicrobial agents, sedatives, and electrolyte preparations) in a 1:1 volume ratio. Among 18 tested drugs, 17 were found to be visually compatible [14]. Although these studies included several agents used in our NICU, such as hydrocortisone sodium succinate and ampicillin sodium, compatibility data for other frequently used drugs remain unavailable.

In our previous study [15], we investigated the compatibility of hydrocortisone sodium succinate (HDC), ampicillin sodium (ABPC), and cefotaxime sodium (CTX) with unfractionated heparin (UFH) under conditions simulating continuous infusion and Y-site administration in the NICU at Tohoku University Hospital. In that study, both physical and chemical compatibilities were evaluated using visual inspection, absorbance measurement, pH determination, and quantitative analysis by HPLC-UV.

In general, the evaluation of admixture stability requires consideration of both physical and chemical compatibility. For physical compatibility, visual inspection of precipitation, turbidity, or discoloration serves as the primary assessment. Turbidity [16,17] and absorbance measurements [18–20] are commonly used for quantitative evaluation. Because pH can affect drug stability and solubility, pH variation before and after mixing is also an important parameter [18–21]. High-performance liquid chromatography (HPLC) is widely employed to quantify the degradation or transformation of active ingredients [21]. In our previous quantitative analysis [15], peak areas at 0 h and 3 h were compared with those of equimolar solutions without UFH. Because no internal standard (IS) was used, the results represented relative rather than absolute changes in analyte concentrations. Nevertheless, the reproducibility was sufficient to evaluate whether HDC, ABPC, and CTX could be safely co-administered via a side port during continuous UFH infusion in the NICU.

In the present study, we aimed to evaluate the physical and chemical compatibility of DOP with injectable drugs frequently used in the NICU at Tohoku University Hospital under conditions simulating continuous infusion and Y-site administration. Using the same analytical approach as in our previous study, we sought to provide practical compatibility data to support safe co-administration of DOP in neonates with limited intravenous access.

2. Materials and Methods

2.1. Drugs

Based on in-hospital dispensing records, injectable drugs frequently used in the NICU were screened. The availability of published admixture compatibility data with DOP was reviewed based on previous studies [13,14] and product information [22–43]. Drugs lacking published compatibility data were selected for further evaluation.

As a result, seven injectable drugs—midazolam (MDZ), dalteparin sodium (DLT), cefazolin sodium hydrate (CEZ), cefepime dihydrochloride hydrate (CFPM), VCM, fosfluconazole (F-FLCZ), and famotidine (FAM)—were ultimately selected as target agents for compatibility testing with DOP (Table 1).

Table 1. Summary of DOP and seven Drugs, additives, diluting solutions, and concentrations.

Classification	Drug	Additives	Solvent and Diluent	Concentration	Abbreviation
Respiratory drugs	Doxapram Hydrochloride Hydrate (Kissei Pharmaceutical Co., Ltd., Matsumoto, Japan)	Chlorobutanol	NS	1.5 mg/mL	DOP
Sedative	Midazolam (Takeda Pharmaceutical Company Limited, Osaka, Japan)	Tonicity agents, pH adjusters	NS	0.18 mg/mL	MDZ
Anticoagulant	Dalteparin Sodium (Sawai Pharmaceutical Co., Ltd., Osaka, Japan)	Sodium chloride, pH adjuster	NS	12.5 IU/mL	DLT
Antibiotics	Cefazolin Sodium Hydrate (NIPRO CORPORATION, Osaka, Japan)	-	NS	100 mg/mL	CEZ
Antibiotics	Cefepime Dihydrochloride Hydrate (Sandoz K.K., Tokyo, Japan)	L-Arginine	NS	100 mg/mL	CFPM
Antibiotics	Vancomycin Hydrochloride (Meiji Seika Pharma Co., Ltd., Tokyo, Japan)	Macrogol, D-mannitol	NS	5 mg/mL	VCM
Antifungal drug	Fosfluconazole (Pfizer Japan, Tokyo, Japan)	pH Adjustment Agent	NS	80 mg/mL	F-FLCZ
Gastric acid suppressants	Famotidine (Nissin Pharmaceutical Co., Ltd., Yamagata, Japan)	Disodium edetate hydrate, acetic acid, phosphoric acid, isotonic agent, pH adjuster	-	1 mg/mL	FAM

Normal saline (NS) was used as the solvent and diluent.

Each drug solution was prepared at the maximum concentration used in the NICU, assuming a neonatal body weight of 1 kg as a standard reference representing very low birth weight and extremely low birth weight infants. DOP and DLT were considered continuous infusion drugs and prepared assuming an infusion rate of 1 mL/h. According to the package insert, DOP is initially administered at 1.5 mg/kg over 1 h [12], and MDZ is recommended at maintenance doses ranging from 0.03 to 0.18 mg/kg/h [39]. VCM should be diluted by adding 0.5 g (potency) to at least 100 mL of infusion fluid [31]. For the other drugs, which can be administered as intravenous boluses, the highest concentrations were prepared by dissolving the drug in the minimum diluent volume or by using the undiluted formulation [26,29,41,43]. The final concentrations used in this study are summarized in Table 1.

For positive control, sodium phosphate corrective injection 0.5 mmol/mL (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) and an 8.5% calcium gluconate injection (Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan) (Ctrl [+]) were used as positive controls [44].

In the HPLC mobile phase, formic acid (Nacalai Tesque, Kyoto, Japan; $\geq 98.0\%$ (T), Specially Prepared Reagent), ultrapure water (Organo Corporation, Tokyo, Japan), and acetonitrile (Kanto Chemical Co., Inc., Tokyo, Japan; for HPLC, $>99.9\%$ (GC)) were used.

2.2. Mixing of Drugs for Preparation of Test Samples

The seven drug solutions were mixed with the DOP solution at a 1:1 volume ratio at room temperature under fluorescent lighting with an average illuminance of 199 lx. In addition, for use as controls in appearance, absorbance and HPLC/UV content measurements, each of the seven solutions was also mixed with NS at a 1:1 ratio. The mixtures were prepared as described in Table 2.

Table 2. Composition of sample mixtures and measurement time points.

Sample	Target Drug	Addition of DOP or NS	Measurement Time
DOP	NS	1.5 mg/mL DOP	0 h
MD	0.18 mg/mL MDZ	NS	0 h
MD-D	0.18 mg/mL MDZ	1.5 mg/mL DOP	0, 3, 24 h
DL	12.5 IU/mL DLT	NS	0 h
DL-D	12.5 IU/mL DLT	1.5 mg/mL DOP	0, 3, 24 h
CZ	100 mg/mL CEZ	NS	0 h
CZ-D	100 mg/mL CEZ	1.5 mg/mL DOP	0, 3 h
CP	100 mg/mL CFPM	NS	0 h
CP-D	100 mg/mL CFPM	1.5 mg/mL DOP	0, 3 h
VC	5 mg/mL VCM	NS	0 h
VC-D	5 mg/mL VCM	1.5 mg/mL DOP	0, 3 h
FF	80 mg/mL F-FLCZ	NS	0 h
FF-D	80 mg/mL F-FLCZ	1.5 mg/mL DOP	0, 3 h
FM	1 mg/mL FAM	NS	0 h
FM-D	1 mg/mL FAM	1.5 mg/mL DOP	0, 3 h

NS: normal saline.

Assuming mixing within a catheter, samples were collected and analyzed immediately after mixing and 3 h post-mixing. Furthermore, for the MDZ and DLT solutions, samples were also collected and analyzed 24 h after mixing, assuming that the two solutions had remained mixed in the same container for 24 h. Samples were stored at room temperature under fluorescent lighting (199 lx) without light protection during the observation period.

2.3. Visual Inspection

All solutions were visually observed for crystal precipitation, suspension, and color change under black and white backgrounds and the photos were taken at the room brightness same as Section 2.2.

2.4. Absorbance Measurement

The ultraviolet–visible (UV–Vis) absorbance of the solutions was measured using Infinite M200 microplate reader (TECAN, Männedorf, Switzerland). Prior to the experiment, the absorbance baseline was set using water, which showed the lowest absorbance at 685 nm. NS was used as the negative control and blank for spectrophotometric analysis. Mixtures exhibiting absorbance values comparable to those of NS were considered free of precipitation or turbidity.

All solutions were sampled in triplicate, measured at the initial and 3 h time points. For the MDZ and DLT solutions, additional samples were collected and analyzed 24 h after mixing. The average values were used for analysis. Crystal precipitation and suspension in the mixtures were statistically assessed using Student's *t*-test to compare absorbance values of each mixture at each time point with those of NS as the negative control. Student's *t*-test was selected as an appropriate method for comparing two independent groups under the assumption of normal distribution. A *p*-value of less than 0.05 was considered statistically significant. Given the small sample size ($n = 3$), statistical significance was interpreted alongside predefined clinical criteria: absorbance values comparable to those of NS were considered acceptable.

2.5. pH Measurement

The pH of the mixture, consisting of DOP solution or NS and the test drug, was measured in triplicate immediately after mixing and again at the times shown in Table 2 using a LAQUA F-71 (HORIBA, Kyoto, Japan). The average values were calculated, and changes in pH over time were statistically evaluated using Student's *t*-test by comparing each time point with the value immediately after mixing. A *p*-value of less than 0.05 was considered statistically significant. Given the small sample size ($n = 3$), pH changes were interpreted in the context of the known physicochemical properties of DOP, which forms a precipitate at pH above 5.8, rather than relying solely on statistical significance.

2.6. Measurement of Changes in Main Content

HPLC/UV was employed to evaluate the main content changes of the seven compounds (excluding DLT) and DOP in each mixture. The HPLC system used was NexeraX2 (SHIMADZU, Kyoto, Japan), and UV analysis was performed with the SPD-M20A (Prominence). For separation, the InertSustain C18 PEEK (2.1 mm i.d. $\times$ 150 mm, 2 μ m, GL Sciences, Tokyo, Japan) was used, with a mobile phase A (formic acid/water [0.1:100, *v/v*]) and mobile phase B (formic acid/acetonitrile, [0.1:100, *v/v*]), respectively. The gradient program was: 0.00–4.00 min, 15% > 75% B; 4.00–4.01 min, 75% > 15% B; post-run, re-equilibration to 15% B. The total chromatographic run time was approximately 6 min. Detection wavelengths were set at 254 nm for the seven compound (excluding DLT) and DOP, respectively. All solutions were analyzed three times immediately after preparation and at the times shown in Table 2.

The mean peak areas were integrated, and the ratio to the control (NS mixture) and the change in ratio (Δ Ratio) at each time point were determined by comparing the peak area obtained from each drug mixed with DOP with that obtained from the same drug mixed with an equal volume of NS.

3. Results

3.1. Change in Appearance with Visual Inspection

The mixture of CFPM and DOP (CP-D) appeared slightly yellow but remained transparent at 3 h after mixing (Supplementary Figure S2). The mixture of CFPM and NS (sample CP in Table 3) also appeared slightly yellow but was transparent throughout the observation period.

All other samples listed in Table 2 were colorless and clear immediately after mixing, and no visible changes, such as precipitation or crystal formation, were observed at any measurement time.

In contrast, the positive control sample became turbid immediately after mixing (Table 3).

Table 3. Change in appearance with visual inspection.

Sample	Initial (0 h) Black/White Background	3 h Black/White Background	24 h Black/White Background
MD	CC/CC		
MD-D	CC/CC	CC/CC	CC/CC
DL	CC/CC		
DL-D	CC/CC	CC/CC	CC/CC
CZ	CC/CC		
CZ-D	CC/CC	CC/CC	
CP	Slightly yellow but transparent/Slightly yellow but transparent		
CP-D	Slightly yellow but transparent/Slightly yellow but transparent	Slightly yellow but transparent/Slightly yellow but transparent	
VC	CC/CC		
VC-D	CC/CC	CC/CC	
FF	CC/CC		
FF-D	CC/CC	CC/CC	
FM	CC/CC		
FM-D	CC/CC	CC/CC	
Ctrl (+)	Turbid/Turbid		

Gray background indicates that no measurement was performed at that time point.

3.2. Absorbance

The UV absorbance of all solutions was measured in triplicate. The mixture of MDZ and DOP (MD-D) showed a decrease in absorbance compared with NS at 3 h point, but no difference was observed at 24 h point. No significant differences were found for the other mixtures when compared with NS (Table 4). Because no increase in absorbance was observed in any of the mixtures compared with NS, this indicates that no significant spectral changes occurred, suggesting the absence of visible or subvisible particulate formation.

Table 4. The absorbance of each sample.

Sample	Initial		3 h		24 h	
	Average (SD)	<i>p</i> -Value [†]	Average (SD)	<i>p</i> -Value [†]	Average (SD)	<i>p</i> -Value [†]
MD	0.041 (0.0011)	0.381				
MD-D	0.041 (0.0006)	0.456	0.040 (0.0009)	0.046 *	0.041 (0.0015)	0.202
DL	0.042 (0.0011)	0.940				
DL-D	0.042 (0.0026)	0.672	0.040 (0.0005)	0.103	0.039 (0.0004)	0.055
CZ	0.041 (0.0005)	0.528				
CZ-D	0.042 (0.0014)	0.852	0.040 (0.0008)	0.163		
CP	0.042 (0.0014)	0.502				
CP-D	0.042 (0.0015)	0.458	0.040 (0.0005)	0.742		
VC	0.041 (0.0009)	0.239				
VC-D	0.042 (0.0021)	0.673	0.040 (0.0013)	0.169		
FF	0.043 (0.0023)	0.568				
FF-D	0.044 (0.0030)	0.431	0.040 (0.0003)	0.213		
FM	0.042 (0.0035)	0.930				
FM-D	0.041 (0.0009)	0.419	0.0040 (0.0003)	0.112		
Ctrl (+)	1.376 (0.0038)					
Ctrl (-)	0.042 (0.0024)					

[†] *p*-value was compared to negative control. The absorbance was measured in triplicate. * indicates significant change. Gray background indicates that no measurement was performed at that time point.

3.3. pH Measurement

A statistically significant increase in pH was observed in the DL-D and VC-D solutions (Table 5). In DL-D, the pH increased by 0.63 at 3 h and by 0.57 at 24 h compared with immediately after mixing, whereas in VC-D, the pH increased by 0.89 compared with the initial value. No significant pH changes were observed in the other solutions within the measurement period.

Table 5. pH changes.

Sample	Initial		After 3 h		After 24 h		
	Average (SD)	Average (SD)	<i>p</i> -Value ‡	ΔpH	Average (SD)	<i>p</i> -Value ‡	ΔpH
MD-D	6.17 (0.329)	6.47 (0.377)	0.251	+0.30	6.54 (0.423)	0.166	+0.37
DL-D	5.24 (0.028)	5.87 (0.094)	<0.001 *	+0.63	5.81 (0.092)	<0.001 *	+0.57
CZ-D	5.32 (0.043)	5.62 (0.053)	0.074	+0.29			
CP-D	4.43 (0.076)	4.48 (0.154)	0.725	+0.06			
VC-D	4.22 (0.001)	5.11 (0.004)	<0.001 *	+0.89			
FF-D	8.25 (0.263)	8.12 (0.216)	0.535	−0.13			
FM-D	6.57 (0.004)	6.77 (0.004)	0.190	+0.20			

‡ *p*-value was compared to the pH at the initial point. The pH was analysed in triplicate. * indicates significant change. Gray background indicates that no measurement was performed at that time point.

3.4. Measurement of Changes in Main Content

The ratios of HPLC/UV peak areas to the control (mean ± SD, *n* = 3) were evaluated for the seven compounds (Table 6) and for DOP (Table 7) in each mixture.

Table 6. Ratios of HPLC/UV peak areas relative to the control for each drug in the drug–DOP mixtures.

Sample	Initial (%)	3 h (%)	ΔRatio (%)	24 h (%)	ΔRatio (%)
MD-D	98.6	104.2	+5.6	106.8	+8.3
DL-D	ND	-	-	-	-
CZ-D	99.0	99.5	+0.5		
CP-D	101.1	108.4	+7.3		
VC-D	101.0	102.3	+1.3		
FF-D	100.6	98.4	−2.2		
FM-D	100.1	100.1	0.0		

Gray background indicates that no measurement was performed at that time point.

Table 7. Ratios of HPLC/UV peak areas relative to the control for DOP in each mixture.

Sample	Initial (%)	3 h (%)	ΔRatio (%)	24 h (%)	ΔRatio (%)
MD-D	100.2	98.1	−2.1	102.2	+2.0
DL-D	100.7	97.0	−3.7	102.7	+2.0
CZ-D	99.7	98.3	−1.4		
CP-D	155.6	169.1	+13.5		
VC-D	110.8	105.6	−5.2		
FF-D	99.7	97.1	−2.6		
FM-D	97.6	100.1	+2.5		

Gray background indicates that no measurement was performed at that time point.

DLT could not be quantified because, as a low-molecular-weight heparin with a broad molecular weight distribution and no distinct UV-absorbing chromophore, it could not be detected as a distinct peak by HPLC.

Except for the CP-D mixture, all mixtures showed changes within 10% relative to the control.

In the CP-D mixture, an unexpected phenomenon was observed in which the DOP peak area increased over time.

Representative chromatograms of each mixture at the initial, 3 h, and 24 h time points are shown in Figures 1 and 2 and Supplementary Figures S3 and S4. Except for the DL-D mixture, all other drugs exhibited single, well-defined peaks at the expected retention times, indicating sufficient selectivity of the analytical method.

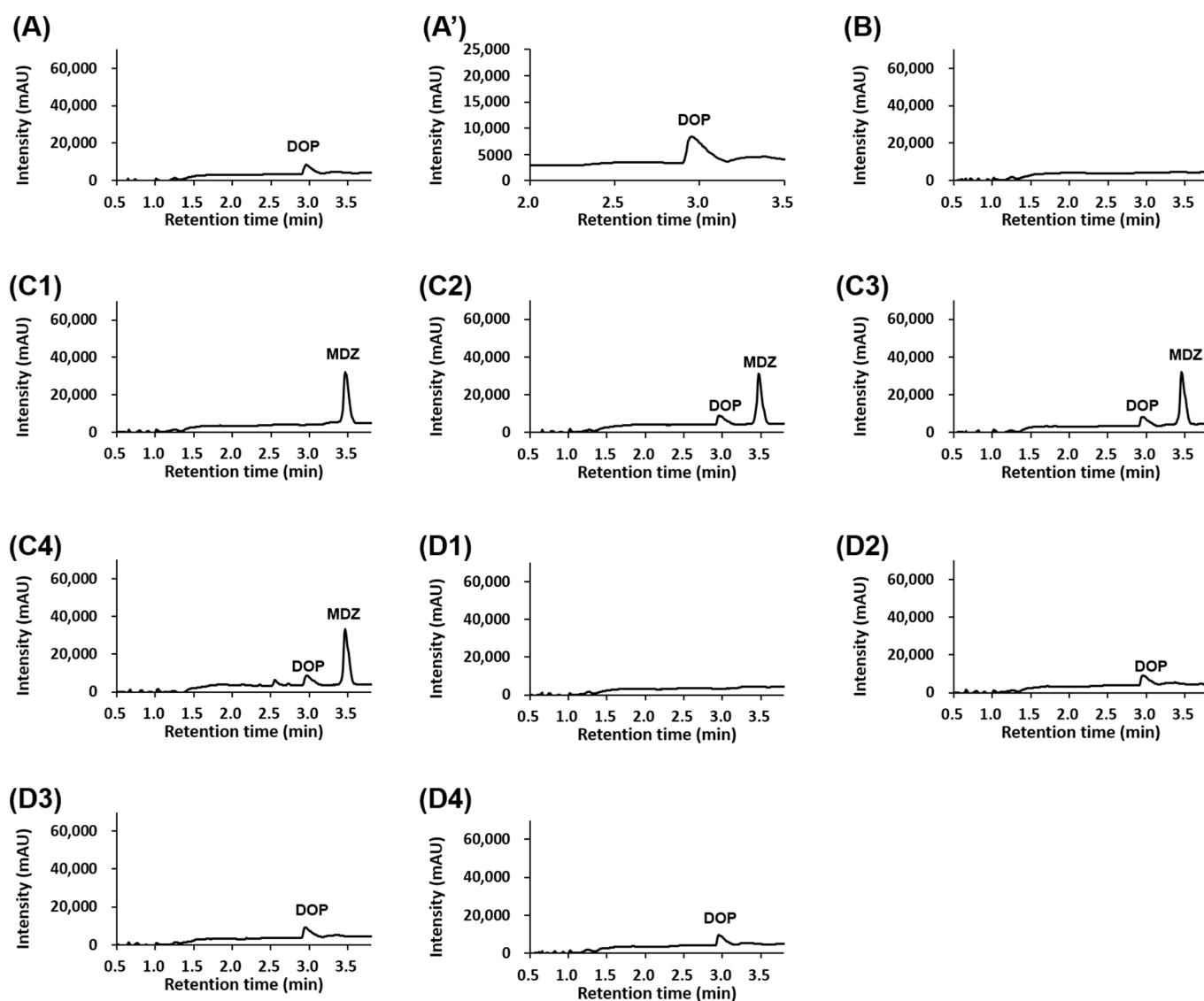


Figure 1. Representative HPLC/UV chromatograms of MD and DL in mixtures with DOP. (A) DOP: 0 h, (A') Enlarged chromatogram of (A) (2.0–3.5 min, up to 25,000 mAU) to visualize the DOP peak, (B) Solvent (NS), (C1) MD: 0 h, (C2) MD-D: 0 h, (C3) MD-D: 3 h, (C4) MD-D: 24 h, (D1) DL: 0 h, (D2) DL-D: 0 h, (D3) DL-D: 3 h, (D4) DL-D: 24 h. Detection wavelengths were set at $\lambda = 254$ nm.

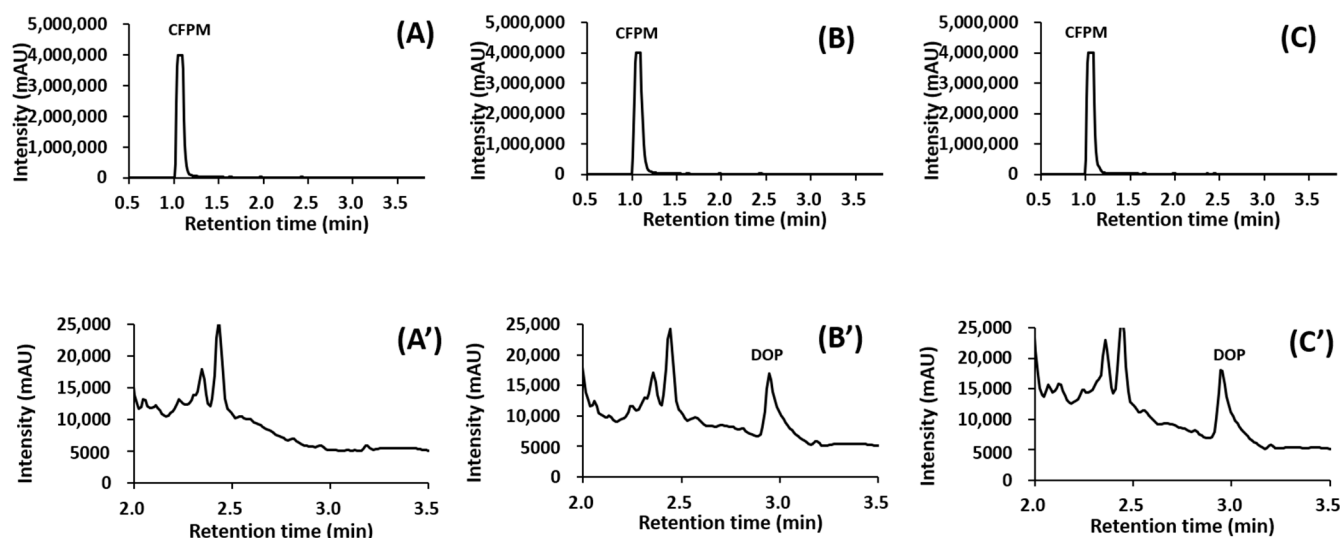


Figure 2. Representative HPLC/UV chromatograms of CP in mixtures with DOP. (A) CP: 0 h, (A') Enlarged chromatogram of (A) (2.0–3.5 min, up to 25,000 mAU) to visualize the DOP peak, (B) CP-D: 0 h, (B') Enlarged chromatogram of (B) (2.0–3.5 min, up to 25,000 mAU) to visualize the DOP peak, (C) CP-D: 3 h. (C') Enlarged chromatogram of (C) (2.0–3.5 min, up to 25,000 mAU) to visualize the DOP peak. Detection wavelengths were set at $\lambda = 254$ nm.

4. Discussion

DOP remains an important therapeutic option in our NICU at Tohoku University Hospital, particularly as a rescue agent for preterm infants unresponsive to caffeine [8–11]. Because of its short half-life, DOP requires continuous intravenous infusion. In this setting, where venous lines are often limited, several medications are commonly co-administered through the same catheter, potentially leading to physicochemical incompatibility.

From a physicochemical standpoint, DOP is classified as a 2-pyrrolidinone derivative, a structural motif that contributes to its central stimulatory activity and moderate chemical stability. In its marketed form, DOP is a hydrochloride salt that remains stable under acidic conditions (pH 3.5–5.0) [12]. However, when the pH rises above approximately 5.8, the hydrochloride salt can dissociate, resulting in conversion to the poorly soluble free-base form and the appearance of a white precipitate. This pH-dependent solubility profile indicates that admixture with alkaline solutions poses a significant risk of physicochemical incompatibility. Previous studies have examined the compatibility of DOP with other injectable drugs. One evaluated 94 agents by assessing visual appearance, pH, osmolality, and drug content [13], while another tested 18 NICU medications under simulated Y-site conditions and found 17 to be visually compatible [14]. However, these studies covered only part of the drugs currently used in NICU, and compatibility data for several frequently administered agents remain unavailable.

The rationale for selecting these seven drugs has been described in the Materials and Methods Section. Evaluating their admixture compatibility with DOP provides clinically relevant data that directly reflect real-world neonatal care and supports safer and more effective pharmacotherapy in infants requiring complex intravenous therapy [45–52].

In this study, the compatibility of DOP with seven selected drugs was evaluated under conditions simulating Y-site co-administration through a side port of the infusion line. Changes were assessed at the initial and 3 h time points. A typical peripherally inserted central venous catheter has an internal diameter of 0.012–0.032 inches (approximately 0.305–0.813 mm) [53], a length of 60 cm, and an internal volume of approximately 0.311 mL. At a slow infusion rate of 0.5 mL/h using a syringe pump [54], the drugs within the catheter are expected to mix within approximately 1 h. Therefore, a 3 h observation period was

considered sufficient to evaluate the compatibility of the admixtures within the catheter. In contrast, because MDZ and DLT are continuously infused in NICU practice—similar to DOP—additional evaluations were performed for up to 24 h to determine whether these drugs could be co-prepared with DOP in the same syringe.

In this study, the miscibility of each admixture was systematically evaluated using visual inspection, UV absorbance measurement, pH measurement, and HPLC/UV analysis, with reference to previous studies [15]. Visual inspection was performed to detect visible incompatibilities such as precipitation, turbidity, or color change in the injectable mixtures. As in many previous compatibility studies [16–21], visual inspection was adopted as the primary screening method. To quantitatively detect subtle or invisible changes, UV absorbance measurement was also performed. The use of UV absorbance for detecting admixture changes has been reported in the methods of Kenneally et al. [18] and Dobson et al. [19]. We applied the same approach by measuring the absorbance at 685 nm, where water showed the lowest absorbance, to quantitatively assess the formation of fine particulate matter in admixtures. Although the European Pharmacopoeia recommends light obscuration or microscopic particle count testing for subvisible particle assessment in parenteral preparations (EP 2.9.19), no official regulatory standard specifies which quantitative method should be used specifically for admixture compatibility testing. The Japanese Pharmacopoeia specifies visual inspection as the standard method for confirming the absence of precipitation or suspension in injectable preparations. Quantitative methods such as turbidity or absorbance measurement have been employed in previous compatibility studies as complementary approaches to visual inspection [18,19]. Except for the positive control, the samples showed transmittance comparable to that of NS, which is known to be clear and particle-free, indicating the absence of turbidity or precipitation during the observation period. pH measurement provides valuable supportive information for interpreting the physicochemical stability of admixtures and has been employed in many previous compatibility studies [18–21]. Although pH measurement alone cannot directly determine physical compatibility, even slight changes may indicate early physicochemical alterations—such as chemical degradation, shifts in ionization state, or a tendency toward precipitation—that precede visible incompatibility. It should be noted that, given the small sample size ($n = 3$), statistically significant differences in absorbance or pH do not necessarily indicate clinically relevant incompatibility. Conversely, the absence of statistical significance does not guarantee compatibility. Therefore, statistical findings were interpreted alongside visual inspection results and the known physicochemical properties of the drugs, particularly the pH-dependent solubility of DOP, which forms a precipitate at pH above 5.8. Monitoring time-dependent pH variation complements visual and spectrophotometric analyses, contributing to a more comprehensive understanding of the stability and compatibility of mixed injections.

In studies evaluating the compatibility of injectable admixtures, physicochemical assessments such as visual inspection, turbidity, and absorbance measurements are commonly performed, whereas the evaluation of chemical stability is often limited to pH measurement. In this study, HPLC/UV analysis was additionally applied to examine changes in the main components and to explore potential degradation or interactions. The mean peak areas were integrated, and the ratios to the control (NS mixture) and their time-dependent changes (Δ Ratio) were calculated to semi-quantitatively assess variations in drug concentrations. Because calibration curves and full validation of the HPLC/UV method were not performed, the results reflect relative rather than absolute changes in drug concentrations. Given that variability of approximately 10% can occur during routine clinical preparation of infusion admixtures [55], this semiquantitative approach was considered sufficient for

the purpose of identifying clinically relevant incompatibilities. Quantitative analysis using an internal standard method would be warranted only if marked changes were observed.

A slight decrease in absorbance was observed in the mixture of MDZ and DOP at the 3 h point; however, this change did not indicate the presence of insoluble particulate matter or precipitation. For MDZ, CEZ, and FAM, no clinically relevant changes were observed in appearance, absorbance, pH, or main content throughout the study period, suggesting that these drugs can be co-administered with DOP under routine clinical conditions. In contrast, the mixtures of DLT and VCM with DOP exhibited a significant increase in pH after 3 h. In the DOP–VCM mixture, no visible changes were detected, and the VCM content did not decrease by more than 5% within 3 h, indicating acceptable compatibility for short-term (≤ 3 h) co-administration. However, the DOP content decreased by 4.9% at the 3 h point, suggesting that the observed pH elevation could affect DOP stability if the admixture is prolonged beyond 3 h. According to the manufacturer's information [12], DOP forms a white precipitate when the pH exceeds 5.8, consistent with previous incompatibility reports with alkaline agents such as aminophylline, furosemide, and thiopental sodium. Although a rise in pH was also observed for the DOP–DLT mixture, no turbidity or absorbance increase occurred, and the DOP content remained within $\pm 5\%$ of the initial value even after 24 h. Because DLT, as a low-molecular-weight heparin, could not be detected as a distinct HPLC peak due to its heterogeneous molecular weight distribution, quantitative evaluation of DLT itself was not possible. The mixture of F-FLCZ and DOP showed no visible, spectral, or pH changes, and the slight 1.6% decrease in F-FLCZ content observed at 3 h (remaining 98.4%) was judged to be clinically acceptable.

Among all combinations, the admixture with CFPM showed the most distinctive finding. At 3 h, only slight yellowing was observed visually, which was considered acceptable as it reflects a characteristic of the formulation. However, HPLC/UV analysis revealed an unexpected and gradual increase in the DOP peak area—approximately 1.6-fold at the initial point and 1.7-fold at 3 h—without any evidence of degradation or the appearance of new peaks. In contrast, the peak area of CFPM itself remained essentially unchanged (101.1% at the initial point and 108.4% at 3 h). These data indicate that the observation cannot be attributed to inter-sample variability, but is instead likely due to an increase in absorbance around the retention time of DOP, suggesting a spectral interaction between DOP and CFPM rather than an actual rise in DOP concentration. Possible mechanisms are proposed to explain this apparent increase in DOP peak area. The admixture exhibited slight alkalinity, likely due to the combined basicity of CFPM (which contains L-arginine) and DOP. Under alkaline conditions, residual silanol groups on the C18 stationary phase become increasingly deprotonated, generating negatively charged sites ($-\text{SiO}^-$). Because CFPM carries a permanent positive charge through its quaternary ammonium moiety, it can interact strongly with these negatively charged silanol groups. As a result, a fraction of CFPM elutes more slowly, appearing as a pronounced tailing peak extending into later retention-time regions. Additionally, the extended CFPM tail may overlap with the retention time of DOP, increasing UV absorbance within the DOP peak window and artificially inflating its measured peak area despite no actual change in DOP concentration. When CFPM and DOP coexist in close proximity in solution, local molecular interactions may alter the microenvironment surrounding DOP. Although direct evidence is lacking, it is generally recognized that the molar absorptivity (ϵ) associated with $\pi \rightarrow \pi^*$ transitions can be influenced by the microenvironment of the chromophore (e.g., solute–solute or solute–solvent interactions) [56,57]. Thus, we cannot exclude the possibility that the close coexistence of DOP and CFPM subtly altered the molar absorptivity of DOP, thereby contributing to the modified chromatographic appearance compared with DOP alone. Taken together, these findings suggest that the increased DOP peak area in the

CFPM–DOP admixture is not attributable to chemical incompatibility or degradation, but rather to pH-dependent chromatographic interactions involving CFPM.

This study also has limitations. Because DLT is a polymeric compound with heterogeneous molecular weight distribution, it could not be quantified by HPLC/UV analysis, and therefore its chemical stability in the admixture could not be assessed. Alternative analytical methods, such as the toluidine blue O colorimetric assay, atomic absorption spectrophotometry, or anti-factor Xa activity measurement using an automated coagulation analyzer, would be required for a complete assessment of DLT stability. Furthermore, all tests were conducted under specific concentrations, solvents, and temperature settings, limiting generalizability to all clinical scenarios. Regarding particulate matter assessment, UV absorbance measurement at 685 nm provides only an indirect evaluation of particle formation. Direct particle count data based on light obscuration or microscopic particle count testing (particles $\geq 10\ \mu\text{m}$ and $\geq 25\ \mu\text{m}$), as recommended by international pharmacopoeial standards, were not obtained in this study. Additionally, although the observation period extended to 24 h for some mixtures, no microbial limit testing or sterility testing was performed. Therefore, the results of this study cannot be used to support the long-term storage or clinical use of these admixtures after preparation. In addition, the stability-indicating nature of the HPLC/UV method was not formally confirmed by forced degradation studies or peak purity assessment. The selectivity was evaluated solely based on the appearance of single, well-defined peaks at expected retention times, and the possibility that minor co-eluting degradation products contributed to the measured peak areas cannot be entirely excluded. Finally, the mechanistic basis of the CFPM–DOP interaction remains incompletely understood and warrants further investigation using comparative UV spectroscopy, mass spectrometry, or NMR-based structural analysis.

5. Conclusions

We systematically evaluated the physicochemical compatibility of seven commonly used NICU medications—MDZ, DLT, CEZ, CFPM, VCM, F-FLCZ, and FAM—under conditions simulating co-administration through the side port of a continuous DOP infusion. Under the specific conditions used in this study (defined concentrations, normal saline as solvent, room temperature, and fluorescent lighting at 199 lx), all admixtures demonstrated clinically acceptable compatibility over a 3 h observation period. In addition, MDZ remained physicochemically stable for up to 24 h under the same conditions. For the DLT–DOP admixture, physical compatibility was confirmed for up to 24 h; however, the chemical stability of DLT could not be assessed by HPLC/UV analysis due to its heterogeneous molecular weight distribution, and conclusions regarding its chemical compatibility are therefore limited. Although the CFPM–DOP admixture produced an artifactual increase in the DOP peak area, this represents an analytical consideration rather than a true incompatibility.

These findings provide physicochemical compatibility data for these drug combinations under the tested conditions and offer a methodological framework for future evaluations of untested drug combinations in the NICU.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/separations13070207/s1>, Figure S1: Flowchart of drug selection for compatibility testing with DOP; Figure S2: Visual appearance of the mixture of CFPM and DOP (CP-D); Figure S3: Representative HPLC/UV chromatograms of CZ and VC in mixtures with DOP; Figure S4: Representative HPLC/UV chromatograms of FF and FM in mixtures with DOP; Table S1: HPLC/UV peak areas of each test drug in the drug–DOP mixtures (mean value with CV%, $n = 3$); Table S2: HPLC/UV peak areas of DOP in the drug–DOP mixtures (mean value with CV%, $n = 3$).

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Abbreviations

The following abbreviations are used in this manuscript:

ABPC	ampicillin sodium
CEZ	cefazolin sodium hydrate
CFPM	cefepime dihydrochloride hydrate
CTX	cefotaxime sodium
DLT	dalteparin sodium
DOP	doxapram hydrochloride hydrate
FAM	famotidine
F-FLCZ	fosfluconazole
HDC	hydrocortisone sodium succinate
HPLC	high-performance liquid chromatography
IS	internal standard
IV	intravenous
NICUs	neonatal intensive care units
NS	normal saline
MDZ	midazolam
UFH	unfractionated heparin
UV-Vis	ultraviolet-visible
VCM	vancomycin hydrochloride

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