Physical compatibility of sulbactam/durlobactam with select intravenous drugs during simulated Y-site administration

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Purpose: Sulbactam/durlobactam is a combination antibiotic designed to target *Acinetobacter baumannii*, including carbapenem-resistant and multidrug-resistant strains. The objective of this study was to determine the physical compatibility of sulbactam/durlobactam solution during simulated Y-site administration with 95 intravenous (IV) drugs.

Methods: Vials of sulbactam/durlobactam solution were diluted in 0.9% sodium chloride injection to a volume of 100 mL (the final concentration of both drugs was 15 mg/mL). All other IV drugs were reconstituted according to the manufacturer's recommendations and diluted with 0.9% sodium chloride injection to the upper range of concentrations used clinically or tested undiluted as intended for administration. Y-site conditions were simulated by mixing 5 mL of sulbactam/durlobactam with 5 mL of the tested drug solutions in a 1:1 ratio. Solutions were inspected for physical characteristics (clarity, color, and Tyndall effect), turbidity, and pH changes before admixture, immediately post admixture, and over 4 hours. Incompatibility was defined as any observed precipitation, significant color change, positive Tyndall test, or turbidity change of ≥0.5 nephelometric turbidity unit during the observation period.

Results: Sulbactam/durlobactam was physically compatible with 38 out of 42 antimicrobials tested (90.5%) and compatible overall with 86 of 95 drugs tested (90.5%). Incompatibility was observed with albumin, amiodarone hydrochloride, ceftaroline fosamil, ciprofloxacin, daptomycin, levofloxacin, phenytoin sodium, vecuronium, and propofol.

Conclusion: The Y-site compatibility of sulbactam/durlobactam with 95 IV drugs was described. These compatibility data will assist pharmacists and nurses to safely coordinate administration of IV medications with sulbactam/durlobactam.

Keywords: *Acinetobacter baumannii*, compatibility, durlobactam, prolonged infusion, turbidity, Y-site

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Beta-lactams are among the most commonly prescribed intravenous antibiotics in the hospital setting.[1,2] Unfortunately, resistance to this antibiotic class is increasing, and newer members of the class are continually introduced with the goal of escaping common resistance mechanisms. *Acinetobacter baumannii* are gram-negative bacteria that predominantly cause nosocomial infections, including ventilator-associated pneumonia, bacteremia, and complicated skin and soft tissue infections.[3-5] Multidrug-resistant (MDR) *A. baumannii* strains pose a threat to human health due to the few antibiotics that retain microbiological activity against them.[3,6]

A. baumannii resistance to β-lactams is predominantly caused by the presence of β-lactamase enzymes that hydrolyze the β-lactam ring.

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Specifically, the de-repression of the AmpC cephalosporinase and the presence of carbapenemases, including Verona integron-encoded metallo-β-lactamase (VIM) and oxacillinase (OXA)-based enzymes (OXA-23, -24, -40, and -58) are the most commonly identified β-lactamases in MDR *A. baumannii* strains.[7-9]

Sulbactam is a semisynthetic, first-generation, class A β-lactamase inhibitor that has activity against *A. baumannii* due to its inhibition of penicillin-binding proteins 1a/b and 3, which are involved in the synthesis of peptidoglycan. However, sulbactam alone is vulnerable to hydrolysis by certain enzyme-mediated resistance mechanisms produced by *A. baumannii*. Durlobactam (investigational name, ETX2514), a novel member of the diazabicyclooctane class of β-lactamase inhibitors, has broad-spectrum inhibitory activity against class A, C, and D serine β-lactamases.[10,11] In a study conducted by Karlowsky and colleagues[12] looking at in vitro activity of sulbactam/durlobactam against a collection of *A. baumannii-calcoaceticus* complex isolates, the addition of 4 μg/mL of durlobactam to sulbactam reduced the sulbactam minimum inhibitory concentration for 50% of isolates (MIC_{50}) from 8 to 1 μg/mL, reduced the MIC_{90} from 64 to 2 μg/mL, and restored susceptibility to 98.3% of tested strains. Therefore, the combination of durlobactam with sulbactam is a promising therapeutic option for the treatment of carbapenem-resistant *A. baumannii*.[13,14]

A recently completed pivotal phase 3 trial (the ATTACK trial) evaluated sulbactam/durlobactam efficacy and safety against that of colistin for the treatment of patients with confirmed hospital/ventilator-acquired pneumonia infections caused by *A. baumannii-calcoaceticus* complex.[15] Patients were randomly assigned 1:1 to sulbactam/durlobactam (1 g administered over 3 hours every 6 hours) or colistin (2.5 mg/kg administered over 30 minutes every 12 hours); all patients received imipenem/cilastatin (1 g administered over 1 hour every 6 hours) as background therapy to cover for polymicrobial infections. During the ATTACK trial, sulbactam/durlobactam was noninferior to colistin for the primary endpoint of 28-day all-cause mortality (19.0% vs 32.3%; absolute difference, –13.2% [95% CI, –30.0% to 3.5%]). Additionally, the incidence of nephrotoxicity was significantly lower with sulbactam/durlobactam than with colistin (13% vs 38%, $P < 0.01$). Sulbactam/drulobactam is now approved in the United States in adults for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex.

Hospitalized patients, especially those with high acuity of illness and MDR organism infections, may have multiple medications being administered via intravenous (IV) access. During clinical development, sulbactam/durlobactam was administered as a 3-hour infusion every 6 hours, thus requiring IV line access for up to 12 hours a day, which could lead to challenges coadministering other IV medications.[16] Y-site administration of 2 IV medications is a valuable option to permit coadministration of IV medications without the need for additional IV access or retiming of multiple medications.

The objective of this study was to determine the physical compatibility of sulbactam/durlobactam in 0.9% sodium chloride injection during simulated Y-site administration with 95 commonly used IV medications (42 antimicrobials and 53 non-antimicrobials).

KEY POINTS

- The physical compatibility of sulbactam/durlobactam with 95 intravenous drugs in 0.9% sodium chloride injection or 5% dextrose in water was determined via assessment of physical characteristics, turbidity, and pH.
- Sulbactam/durlobactam was physically compatible over 4 hours with 86 of 95 drugs tested (90.5%); main reasons for incompatibility were increased turbidity and change in physical characteristics.
- The compatibility data will assist pharmacists and nurses in making informed decisions about safely coadministering sulbactam/durlobactam with other medications.

Methods

Sulbactam and durlobactam[a] were provided by the study sponsor (Entasis Therapeutics) in separate single-dose vials of 1 g of sulbactam powder and 0.5 g of durlobactam powder for reconstitution. Sulbactam vials were reconstituted with 5 mL of sterile water for injection,[b] and durlobactam vials were reconstituted with 2.5 mL of sterile water for injection. Once the drugs were fully dissolved, 7.5 mL of each solution was diluted in commercially available 0.9% sodium chloride for injection[c] to a total volume of 100 mL. The final concentration was 15 mg/mL of each component drug (designated as 15-15 mg/mL hereafter), which represented the IV admixture concentration for the highest proposed doses of sulbactam and durlobactam (1.5 g for both) for patients with a creatinine clearance of >130 mL/min. All prepared admixtures of sulbactam/durlobactam were refrigerated (2-8 °C) for up to 4 hours before the start of Y-site compatibility studies at room temperature. The concentrations for secondary drugs selected were the highest concentrations routinely used clinically. Reconstitutions of secondary drugs were performed according to the manufacturer's recommendation using commercially available sterile water for injection or 0.9% sodium chloride injection, with further dilution in 0.9%

sodium chloride injection[d] in IV bags to a total volume of 50 mL. Ciprofloxacin and linezolid were only available as premixed formulations in 5% dextrose in water and were not further diluted in 0.9% sodium chloride injection. Prior to dilution of secondary drugs, a volume equal to the amount of drug to be added was removed from the IV bag.

Simulation of Y-site administration to simulate inline mixing of 2 drugs in a 1:1 ratio has been previously established.[17] Y-site administration was simulated by mixing 5 mL of diluted sulbactam/durlobactam with 5 mL of each secondary IV medication in a colorless 15-mL, borosilicate glass, screw-cap culture tube with a propylene cap.[e] Four test solutions were prepared to ensure reproducibility for each drug combination, with 2 of 4 test tubes mixed in reverse order. All drugs were freshly prepared and filtered through a 0.22-µm filter[f] as they were introduced into their respective culture tubes to remove particulate matter, except albumin and propofol, which were filtered using a 5-µm filter[g] to prevent filtering of protein and oil phase out of the mixture, respectively. The 10-mL solutions were compared against controls prepared with 5 mL of sulbactam/durlobactam 15-15 mg/mL and 5 mL of 0.9% sodium chloride for injection.

All sample tubes were assessed for visual physical characteristics, turbidity, and pH prior to admixture, immediately upon mixing, and at 4 hours. Mixtures deemed incompatible at 4 hours were repeated in entirety and further assessed at the 0.5- and 2-hour time points. Assessment time points were selected to reflect the recommended infusion time for sulbactam/durlobactam (3 hours) plus an additional 1 hour to account for clinical scenarios that could disrupt or extend the infusion time. Tubes were inverted 3 times to mobilize precipitates (if present) before visual physical characteristic and turbidity assessments. Samples were stored per manufacturer recommendations prior to admixture and at room temperature (20-22 °C) for the entire 4-hour experiment. Samples that required protection from light per manufacturer recommendations were covered with aluminum foil.

Physical characteristics assessment was completed with the unaided eye against a white and black background, and the Tyndall effect was assessed using a 380- to 630-nm, <5mW red laser[h] to aid in visualization of suspended particulate matter.[18-20] As this test allows for detection of small suspended particles within a medium as the scattering of a beam occurs, it further aids in detection of particles that would otherwise not be visible to the unaided eye.[21] For the second assessment, a laboratory-grade turbidimeter[i] was used per manufacturer instructions to record the turbidity of each sample after visual physical characteristic assessment and as described in USP chapter <855>.[22] The turbidimeter was calibrated with primary standards that ranged from less than 0.1 nephelometric turbidity unit (NTU) to 4,000 NTU,[j] and calibration was checked before use with secondary standards ranging from 0 NTU to 10,000 NTU.[k] The NTU, a measure of turbidity within a fluid or the presence of suspended particles in a solution, has been extensively used in previous compatibility studies. The turbidity of each drug was assessed as described previously and in triplicate per sample tube. Incompatibilities for the assessments described above were defined as the appearance of any visible particulate matter, haze, color change, or change in measured turbidity of ≥0.5 NTU in any of the 4 sample tubes.[23]

Lastly, pH measurements were performed using a pH meter[l] to assess whether observed incompatibilities might be due to an acid-base disruption. The pH measurements were completed by taking 0.5 mL from the bag prior to admixture and passing the solution through a 0.22-µm filter,[f] while measurements of pH post admixture were completed by taking 0.5-mL aliquots from each 10-mL sample tube. Calibration of the pH meter occurred before each experiment using pH 4, pH 7, and pH 10 standards.

Propofol is a lipid emulsion with a milky white appearance; therefore, an alternate procedure was used to evaluate physical compatibility.[24] Samples were prepared in 15-mL colorless, propylene plastic centrifuge tubes,[m] and a total of 16 test mixtures were prepared and filtered as previously mentioned for all time points (4 tubes per time point; immediately after mixture and at 0.5 hour, 2 hours, and 4 hours). Each tube contained 5 mL of sulbactam/durlobactam (15-15 mg/mL) and 5 mL of filtered propofol, and mixing was completed simultaneously for all samples. Each set was centrifuged at 12,000 rpm for 15 minutes at its designated time point and compared to a 10-mL propofol control. Visual sample inspection was completed prior to admixture and post centrifugation. The pH was measured as mentioned previously. Incompatibility of propofol was defined as formation of precipitate deposited at the bottom of the centrifugation tube or evidence of compromised emulsion. After centrifugation, an intact emulsion is expected to be observed via formation of a white fat plug that settles in the upper layer while the aqueous layer remains in the bottom of the tube. If the emulsion is broken, a layer of free oil compromising the integrity of the fat plug is observed.[18,19,24]

Results and discussion

Upon reconstitution with sterile water for injection, the sulbactam solution was clear and colorless, while the durlobactam solution was dark brown. When both components were mixed at a concentration of 15-15 mg/mL, the final solution was a light yellow to light brown, free-flowing solution. Diluted sulbactam/durlobactam in 0.9% sodium chloride for injection had a baseline mean (SD) turbidity of 0.843 (0.01) NTU and a mean (SD) pH of 6.43 (0.01). The control solution containing an additional 5 mL of 0.9% sodium chloride for injection was light yellow to light brown in color and had a baseline mean (SD) turbidity of 0.593 (0.01) NTU and a mean (SD) pH of 6.45 (0.01). Mean (SD) turbidity at 0.5 and 2 hours

Table 1. Parenteral Drugs Assessed for Physical Compatibility With Sulbactam/Durlobactam (15-15 mg/mL) in 0.9% Sodium Chloride Injection

Drug and concentration	Manufacturer (lot)	Observation
Albumin 250 mg/mL[a]	Baxalta (LB065277)	Incompatible
Amiodarone hydrochloride 2 mg/mL	Mylan (220126)	Incompatible
Amikacin sulfate 10 mg/mL	Avet Pharmaceuticals (ES220139)	Compatible
Anidulafungin 0.77 mg/mL	Pfizer (DX0909)	Compatible
Azithromycin 2 mg/mL	Sun Pharma (HAD1227A)	Compatible
Aztreonam 20 mg/mL	Fresenius Kabi (6027250)	Compatible
Bumetanide 0.25 mg/mL[a]	Athenex Pharmaceuticals (E036A007)	Compatible
Calcium chloride 20 mg/mL	Hospira (38250DK)	Compatible
Calcium gluconate 20 mg/mL	Fresenius Kabi (6026010)	Compatible
Caspofungin acetate 0.5 mg/mL	Athenex Pharmaceuticals (AAF120)	Compatible
Cefazolin 20 mg/mL	Sagent (2019E0)	Compatible
Cefepime hydrochloride 40 mg/mL	Premier Pro Rx (0008E12)	Compatible
Cefotetan disodium 20 mg/mL	Fresenius Kabi (0001E21)	Compatible
Cefiderocol 20 mg/mL	Shionogi (0020)	Compatible
Cisatracurium 0.4 mg/mL	Abbvie (A000042820)	Compatible
Cefoxitin 20 mg/mL	Premier Pro Rx (2002E1)	Compatible
Ceftaroline fosamil 12 mg/mL	Allergan Inc (0002E26)	Incompatible
Ceftazidime 40 mg/mL	Hospira (LT0951)	Compatible
Ceftazidime/avibactam (40 mg/mL; 10 mg/mL)	Allergan Inc (2008E2)	Compatible
Ceftolozane/tazobactam (20 mg/mL; 10 mg/mL)	Merck (SP1786)	Compatible
Ceftriaxone sodium 20 mg/mL	Apotex (1M0645A32)	Compatible
Cefuroxime 30 mg/mL	Sagent (0002E2)	Compatible
Ciprofloxacin 2 mg/mL	Claris Baxter (A0F0121A)	Incompatible
Colistimethate sodium 4.5 mg/mL[b]	Fresenius Kabi (6126856)	Compatible
Daptomycin 20 mg/mL	Hospira (KZ029)	Incompatible
Dexamethasone sodium phosphate 1 mg/mL[c]	Fresenius Kabi (6128116)	Compatible
Dexmedetomidine hydrochloride 0.004 mg/mL	Hospira (37315CD)	Compatible
Digoxin 0.25 mg/mL[a]	West-Ward (2203030.1)	Compatible
Diltiazem hydrochloride 5 mg/mL[a]	Hikma injectables (062098)	Compatible
Diphenhydramine hydrochloride 50 mg/mL[a]	Mylan (21124)	Compatible
Dobutamine hydrochloride 4.1 mg/mL	Hospira (GH2441)	Compatible
Dopamine hydrochloride 0.8 mg/mL	Hospira (40071DK)	Compatible
Doxycycline hyclate 1 mg/mL	Fresenius Kabi (6027244)	Compatible
Epinephrine hydrochloride 0.016 mg/mL	BPI Labs (I120E003A1)	Compatible
Ertapenem 20 mg/mL	Par Pharmaceutical (W011193)	Compatible
Eravacycline 0.6 mg/mL	Tetraphase Pharmaceuticals (AR6450B)	Compatible
Esmolol hydrochloride 10 mg/mL[a]	Mylan (2203D4)	Compatible

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Table 1. Parenteral Drugs Assessed for Physical Compatibility With Sulbactam/Durlobactam (15-15 mg/mL) in 0.9% Sodium Chloride Injection

Drug and concentration	Manufacturer (lot)	Observation
Esomeprazole sodium 0.8 mg/mL	Slate Run Pharmaceuticals (120340400)	Compatible
Famotidine 4 mg/mL	Fresenius Kabi (6128308)	Compatible
Fentanyl 0.05 mg/mL[a]	Fresenius Kabi (6026241)	Compatible
Fluconazole 2 mg/mL	Sagent (20522)	Compatible
Fosphenytoin sodium 25 mg/mL[d]	Pfizer (FY9922)	Compatible
Furosemide 3 mg/mL	Wockhardt (146106)	Compatible
Gentamicin sulfate 5 mg/mL	Fresenius Kabi (6128715)	Compatible
Heparin sodium 1000 units/mL	Fresenius Kabi (6027289)	Compatible
Hydrocortisone sodium succinate 1 mg/mL[e]	Pfizer (FW3866)	Compatible
Hydromorphone hydrochloride 1 mg/mL	Teva (41025CF)	Compatible
Imipenem/cilastatin (5 mg/mL; 5 mg/mL)	Fresenius Kabi (0002E21)	Compatible
Imipenem/cilastatin/relebactam (5 mg/mL; 5 mg/mL; 2.5 mg/mL)	Merck (U013203)	Compatible
Insulin human regular 1 unit/mL	Eli Lilly (0483145C)	Compatible
Isavuconazonium sulfate 0.8 mg/mL[f]	Astellas Pharmaceuticals (941789)	Compatible
Labetalol hydrochloride 2 mg/mL	Hospira (GK7284)	Compatible
Levofloxacin hydrochloride 5 mg/mL	Akorn (061412A)	Incompatible
Lidocaine hydrochloride 8 mg/mL	Fresenius Kabi (6129096)	Compatible
Linezolid 2 mg/mL	Auromedics (LZ22037)	Compatible
Lorazepam 1 mg/mL	West-Ward (042077)	Compatible
Magnesium sulfate 100 mg/mL	Fresenius Kabi (6026685)	Compatible
Mannitol 20%[a]	ICU Meds (5859363)	Compatible
Meperidine hydrochloride 10 mg/mL	Hospira (42570CL)	Compatible
Meropenem 20 mg/mL	Auromedics (MI0122031A)	Compatible
Meropenem/vaborbactam (8 mg/mL; 8 mg/mL)	Melinta Therapeutics (0008E0)	Compatible
Mesna 20 mg/mL	Sagent (AGF202)	Compatible
Methylprednisolone sodium succinate 20 mg/mL[g]	Pfizer (FR5113)	Compatible
Metoclopramide hydrochloride 0.2 mg/mL	Hospira (FY0220)	Compatible
Metronidazole 5 mg/mL	Baxter (P435956)	Compatible
Midazolam hydrochloride 1 mg/mL	Premier Pro Rx (061110Z)	Compatible
Micafungin sodium 4 mg/mL	Hikma injectables (2242011.1)	Compatible
Milrinone lactate 0.2 mg/mL	Meitheal Pharmaceuticals (A8C0209E)	Compatible
Minocycline 0.4 mg/mL	Melinta Therapeutics (00011)	Compatible
Morphine sulfate 1 mg/mL	Piramal (AR4952B)	Compatible
Naloxone hydrochloride 0.04 mg/mL	Akorn (061272A)	Compatible
Nicardipine hydrochloride 0.1 mg/mL	West-Ward (P0001731)	Compatible
Nitroglycerin 0.4 mg/mL	Baxter (G156813)	Compatible

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Table 1. Parenteral Drugs Assessed for Physical Compatibility With Sulbactam/Durlobactam (15-15 mg/mL) in 0.9% Sodium Chloride Injection

Drug and concentration	Manufacturer (lot)	Observation
Norepinephrine bitartrate 0.032 mg/mL	Amneal (AP220265)	Compatible
Octreotide 0.004 mg/mL	Hikma injectables (082088)	Compatible
Omadacycline 2 mg/mL	Paratek Pharmaceuticals (W003670)	Compatible
Ondansetron hydrochloride 0.16 mg/mL	Avet Pharmaceuticals (183203)	Compatible
Pantoprazole sodium 0.4 mg/mL	Pfizer (528086)	Compatible
Penicillin G potassium 100,000 units/mL	Athenex Pharmaceuticals (1F05GU)	Compatible
Phenylephrine hydrochloride 1 mg/mL	Exela Pharmaceutical Sciences (00050A)	Compatible
Phenytoin sodium 10 mg/mL	West-Ward (101102)	Incompatible
Piperacillin/tazobactam (40 mg/mL; 5 mg/mL)	Apotex (AK204005F1)	Compatible
Plazomicin 24 mg/mL	Achaogen (EX5-240)	Compatible
Polymyxin B sulfate 2000 units/mL	Fresenius Kabi (6128746)	Compatible
Potassium chloride 0.1 mEq/mL	Fresenius Kabi (6027089)	Compatible
Potassium phosphates 0.3 mmol/mL	CMP Pharmaceuticals (CR86)	Compatible
Propofol 10 mg/mL[a]	Fresenius Kabi (10RB6221)	Incompatible
Rocuronium bromide 5 mg/mL	Fresenius Kabi (6028138)	Compatible
Sodium bicarbonate 1 mEq/mL[a]	Exela Pharmaceutical Sciences (P0001853)	Compatible
Sodium phosphates 0.3 mmol/mL	Fresenius Kabi (6025836)	Compatible
Tigecycline 1 mg/mL	Accord (R2200936)	Compatible
Tobramycin sulfate 5 mg/mL	Hospira (378117DK)	Compatible
Vancomycin 5 mg/mL	Mylan (7607573)	Compatible
Vasopressin 1 unit/mL	Amphastar Pharmaceuticals (VA001F2)	Compatible
Vecuronium bromide 1 mg/mL[a]	Auromedics (VB22019)	Incompatible

[a]Undiluted product was used.
[b]Concentration expressed in terms of colistin.
[c]Concentration expressed in terms of dexamethasone phosphate.
[d]Concentration expressed in terms of phenytoin sodium equivalents.
[e]Concentration expressed in terms of hydrocortisone.
[f]Concentration expressed in terms of isavuconazole.
[g]Concentration expressed in terms of methylprednisolone.

remained at 0.584 (0.01) NTU and, at 4 hours, increased to 0.616 (0.01) NTU. The mean (SD) pH at 4 hours was 6.37 (0.01). Immediately post admixture (ie, at 0 hours) and at 0.5, 2, and 4 hours, no notable color changes, haziness, or visible particulate matter were observed with the unaided eye in the control solutions.

The final compatibility results for the total of 95 medications tested are displayed in Table 1. Eighty-six of the tested drugs (90.5%) were compatible with sulbactam/durlobactam over the 4-hour experiment, including 38 of 42 antimicrobials (90.5%). Table 2 describes the physical characteristics of the 9 incompatible drugs.

The most common reason for incompatibility was a change in turbidity of ≥0.5 NTU (observed in all samples). The second most common reason for incompatibility was a change in the solutions' physical appearance at any given time point. Albumin, amiodarone, ciprofloxacin, and phenytoin all showed a change in physical appearance when assessed with the unaided eye. Specifically, amiodarone and ciprofloxacin had crystal formation present at 4 hours, albumin became cloudy upon admixture, and phenytoin had gross precipitate formation upon admixture. Admixture of amiodarone, ciprofloxacin, albumin, and phenytoin also resulted in a positive Tyndall effect. In contrast, mixing of sulbactam/durlobactam with both ceftaroline fosamil and daptomycin

Table 2. Physical and pH Characteristics of Drugs Incompatible With Sulbactam/Durlobactam (15-15 mg/mL) in 0.9% Sodium Chloride Injection

	Physical characteristics (sulbactam/durlobactam baseline [preadmixture] characteristics: clear, particulate free, no haziness or Tyndall effect, light yellow to light brown in color)				pH, mean (sulbactam/durlobactam baseline [preadmixture] pH: 6.18)			
Drug	**0 h[a]**	**0.5 h[a]**	**2 h[a]**	**4 h[a]**	**Baseline (preadmixture)**	**0 h[b]**	**4 h[b,c]**	**Absolute difference[d]**
Albumin	Cloudy and Tyndall positive; turbidity ≥5 NTU	NA	NA	Cloudy and Tyndall positive; turbidity ≥5 NTU	6.95	6.87	6.82	–0.13
Amiodarone hydrochloride	Clear and Tyndall negative; turbidity ≥0.5 NTU	NA	NA	Precipitation of crystals and Tyndall positive; turbidity ≥0.8 NTU	4.73	6.09	6.06	1.33
Ceftaroline Fosamil	No change relative to control	Clear and Tyndall positive (2 of 4 tubes); turbidity ≥0.8 NTU	Clear and Tyndall positive; turbidity ≥2 NTU	Clear and Tyndall positive; turbidity ≥4 NTU	5.08	5.24	5.25	0.17
Ciprofloxacin	Clear and Tyndall negative; turbidity ≤ 0.5 NTU	NA	NA	Gross crystal formation and Tyndall Positive; turbidity ≥0.8 NTU	4.11	5.08	5.19	1.08
Daptomycin	Clear and Tyndall positive; turbidity ≥0.6 NTU	Clear and Tyndall positive; turbidity ≥0.6 NTU	Clear and Tyndall positive; turbidity ≥0.7 NTU	Clear and Tyndall positive; turbidity ≥0.7 NTU	4.51	4.65	4.68	0.17
Levofloxacin	Clear and Tyndall negative; turbidity ≥0.5 NTU	NA	NA	Clear and Tyndall negative; turbidity ≥0.5 NTU	4.78	5.46	5.52	0.74
Phenytoin sodium	Cloudy with gross sedimentation; Tyndall positive; turbidity >500 NTU	NA	NA	Cloudy with gross sedimentation; Tyndall positive; turbidity >1,400 NTU	10.39	9.94	8.36	–2.03
Propofol	Compromised emulsion	Compromised emulsion	NA	NA	7.51	6.61	6.61[b]	–0.9
Vecuronium	Clear and Tyndall negative; turbidity ≤0.5 NTU	NA	NA	Clear and Tyndall negative; turbidity ≥0.5 NTU	3.93	4.25	4.34	0.41

Abbreviations: NA, not assessed; NTU, nephelometric turbidity unit.
[a]Changes observed in all tubes unless otherwise noted.
[b]Mean pH in all 4 tubes.
[c]Second pH measurement conducted at 4 hours for all drugs except propofol, which was conducted at 0.5 hours.
[d]Absolute difference is the baseline of test agent (preadmixture pH) compared to pH at 4 hours; mean taken from all 4 tubes.

resulted in clear, particulate-free solutions on inspection with the unaided eyes, but there was a positive Tyndall effect. Admixture of vecuronium or levofloxacin with sulbactam/durlobactam resulted in a clear, particulate-free solution and a negative Tyndall effect immediately post admixture and at 4 hours, but an increase in turbidity was observed at the measurement time points.

While there is a lack of studies describing why the incompatibilities described above may occur, there are several explanations that can be hypothesized. When considering incompatibilities of drug solutions and their visible or nonvisible precipitates, one must consider the chemical interactions (intermolecular and interionic forces).[25] Possible causes of precipitation are acid-base reactions (these are the most common), nondissociated salts of organic ions, salting out, salts of inorganic divalent ions, desolvation of nonionized organic drugs, organic ion/inorganic ion salts, and acid-base conjugate pairs.[25] While the factors mentioned above are of relevance, they were not thoroughly studied within our study design; however, given that acid-base perturbations may be a cause of incompatibilities, pH was assessed (Table 2). Shifts in pH may drive precipitate formation due to formation of ionized versus un-ionized drug.[25,26] For instance, premixed solutions of ciprofloxacin in 5% dextrose had a mean (SD) pH of 4.11 (0.02), which increased once they were mixed with sulbactam/durlobactam to 5.08 (0.03) immediately post admixture and further increased to 5.19 (0.03), with an overall mean change in pH of 1.08. Ciprofloxacin has no crystal precipitate formation in acidic conditions, but in alkaline pH precipitation of crystals is observed.[27,28] In the case of amiodarone, the baseline (preadmixture) mean (SD) pH was 4.73 (0.02); immediately upon admixture, the pH increased to 6.09 (0.02) and remained constant at 6.06 (0.01) at 240 minutes, with an overall shift in pH of 1.33. Phenytoin had a baseline (preadmixture) pH of 10.39 (0.03), and upon admixture the pH decreased to 9.94 (0.09) and further decreased to 8.36 (0.05), with an overall mean shift in pH of –2.03. Amiodarone crystal precipitation is driven by alkaline pH conditions,[29-31] while phenytoin gross precipitation is manifested by a shift towards acidic pH.[32,33]

All other incompatible medications (albumin, ceftaroline fosamil, daptomycin, levofloxacin, and vecuronium) showed a minor change in pH, as shown in Table 2, which may help explain the incompatibilities observed. In addition, propofol has been demonstrated to have poor compatibility when Y-sited with other medications, as it is only available as a lipid emulsion.[24] In our study propofol exhibited oiling out of cracked emulsions immediately post admixture and at the 0.5-hour time point. Its mean (SD) pH at baseline (before admixture) was 7.51 (0.01), and immediately post admixture and at 0.5 hour, the pH decreased to 6.61 (0.01). Propofol incompatibility was not surprising, as it has been previously reported that changes in pH, temperature, electrostatic and mechanical barrier disruptions, and electrolyte concentrations can disturb the stability of its lipid emulsion and induce degradation.[34,35]

Conclusion

Sulbactam/durlobactam at a concentration of 15-15 mg/mL was physically compatible with 38 of 42 antimicrobials (90.5%) and, overall, compatible with 86 of 95 drugs tested (90.5%). The results not only highlight its physical compatibility with other agents but also provide evidence to suggest flexibility in the clinical setting when considering Y-site administration durations for up to 1 hour beyond the recommended 3-hour sulbactam/durlobactam infusion interval. The availability of data on the physical compatibility of sulbactam/durlobactam with other IV medications when given via simulated Y-site administration will allow pharmacists and nurses to make informed decisions about safely coadministering sulbactam/durlobactam with other medications.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Disclosures

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[a]Entasis Therapeutics, Waltham, MA; sulbactam, lot 2011184 (manufactured April 9, 2022; durlobactam, lot B20050044 (manufactured April 9, 2022).
[b]ICU Medical, Lake Forest, IL, lot 5240821.
[c]ICU Medical, lot 5868542.
[d]B. Braun Medical Inc., Bethlehem, PA, lot J2D731.
[e]Fisher Scientific, Waltham, MA.
[f]Whatman Uniflo PVDF syringe filter, Cytiva, Marlborough, MA, lot 220312-419-A.
[g]Baxter Healthcare, Deerfield, IL.
[h]Alpec, Ramer, AL.
[i]Model 2100 N, Hach Company, Loveland, CO.
[j]StabCal Calibration set, Hach Company.
[k]Gelex secondary turbidity standard kit, Hach Company, lot A2133.
[l]Orion 320 PerpHecT LogR, Thermo Fisher Scientific, Beverly, MA.
[m]Thomas Scientific, Swedesboro, NJ, lot 12427.

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