



Chemical Stability of Ceftolozane/Tazobactam in Polyvinylchloride Bags and Elastomeric Pumps



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ABSTRACT

Background: Elastomeric pumps are often used to administer intravenous antibiotics in the outpatient setting, but effective infusion requires that the drug remain stable in solution throughout the procedure. **Objective:** To determine the chemical stability of ceftolozane/tazobactam when reconstituted and stored over an extended time in the AccuFlo (EMED Technologies, El Dorado Hills, California) and I-Flow Homepump Eclipse (Halyard, Alpharetta, Georgia) elastomeric pumps compared with the results of the label-supporting studies in polyvinylchloride (PVC) bags.

Methods: Two ceftolozane/tazobactam dosages were tested for the elastomeric pump studies: 1500 mg (1 g ceftolozane/0.5 g tazobactam) and 150 mg (100 mg ceftolozane/50 mg tazobactam). The solution hold time was evaluated for 10 days at 5°C ($\pm 3^\circ\text{C}$) (tolerance ± 3 hours) and for 1 day (24 hours) at ambient room temperature (tolerance ± 3 hours). Results of a previously conducted label-supporting PVC intravenous bag study were used as a comparator.

Results: At each time point, the visual appearance of all pump and PVC bag solutions remained clear and free of visible particulates, and subvisible particulate matter did not differ significantly between the initial time point and at 10 days. No notable changes in pH in any of the pump or PVC solutions occurred throughout the study. Recovery of ceftolozane and tazobactam was greater than 93% and 94%, respectively, for all samples (elastomeric pump and PVC bag) at 10 days.

Conclusions: Ceftolozane/tazobactam remains physically and chemically stable for at least 7 days, as indicated on the US label, when reconstituted, diluted, and stored in the AccuFlo and I-Flow Homepump Eclipse elastomeric pumps and in PVC intravenous bags.

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Introduction

The novel β -lactam/ β -lactamase inhibitor combination ceftolozane/tazobactam is approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections^{1,2} and is currently being assessed in an ongoing Phase III clinical trial for the treatment of nosocomial pneumonia (ClinicalTrials.gov identifier NCT02070757). The approved intravenous dose of ceftolozane/tazobactam is 1.5 g (1 g ceftolozane/0.5 g tazobactam) administered q8h for up to 7 days for complicated urinary tract infections and up to 14 days for complicated intra-abdominal infections.²

After reconstitution in water for injection or in normal saline (NS), with further dilution of ceftolozane/tazobactam in either NS or 5% dextrose in water (D5W), according to the US label,² the

solution is stable for 24 hours when stored at room temperature (23°C–27°C) or for 7 days when stored under refrigeration (2°C–8°C) in polyvinylchloride (PVC) intravenous bags. Although additional markets have approved a period of 10 days when the solution is stored under refrigeration at 2°C to 8°C, and all chemical data in the PVC bags support a 10-day hold, the US Food and Drug Administration restricted the label to 7 days because of concern regarding proper aseptic technique and the introduction of microbes during preparation (personal communication, Elizabeth G. Rhee, Merck & Co., Inc.).

In outpatient settings, elastomeric pumps are often used for administration of intravenous antibiotics.^{3,4} There is substantial interest in demonstrating compatibility with outpatient infusion systems for both standard-dose administration and continuous or prolonged infusion. Continuous or prolonged infusion is also of interest for β -lactams, such as ceftolozane/tazobactam, to ensure the attainment of pharmacokinetic/pharmacodynamic targets (the time that drug concentrations are maintained across the dosing interval at a level above the minimum inhibitory concentration) in certain clinical settings. However, effective infusion with the

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elastomeric pump requires that the drug remain stable in solution throughout the duration of the infusion^{5,6} to ensure adequate delivery of active drug while avoiding patient exposure to toxic degradation products.⁷

This study investigated the chemical stability of ceftolozane/tazobactam when reconstituted and stored for an extended time in the AccuFlo (model CT-1000-10; EMED Technologies, El Dorado Hills, California) and I-Flow Homepump Eclipse elastomeric pumps (model E101000; Halyard, Alpharetta, Georgia) and compared the result with the results of the label-supporting studies² in PVC bags.

Materials and Methods

In this study, 2 dilution solutions were evaluated in the elastomeric pump: 0.9% NS and D5W. Two doses were tested at each solution/temperature combination for the elastomeric pump studies: 1500 mg (1 g ceftolozane/0.5 g tazobactam; Dose 1) and 150 mg (100 mg ceftolozane/50 mg tazobactam; Dose 2) bracketed concentrations that would be prepared in an individual elastomeric pump depending on the renal function of the patient.

Results of a previously conducted label-supporting PVC intravenous bag study are reported here as a comparator. The upper dose evaluated was 4500 mg as a bracketed concentration to support the administration of a 24-hour ceftolozane/tazobactam infusion regimen (3 × 1500 mg) prepared in a single intravenous bag. Therefore, direct comparison between the elastomeric pumps and the intravenous bag is available at the 150-mg dose.

Drug product preparation

Before introduction of the solution into the elastomeric pumps, the study drug was reconstituted for injection in 100-mL IV bags containing either NS or D5W (B. Braun Medical Inc, Bethlehem, Pennsylvania) as follows: 10 mL NS or 10 mL D5W was withdrawn from each intravenous bag and discarded, and vials of ceftolozane/tazobactam were each reconstituted with 10 mL NS. For Dose 1, the entire contents of a reconstituted vial were withdrawn and transferred by syringe to each intravenous bag for a final volume of ~101.4 mL. For Dose 2, 1.1 mL from each reconstituted vial was transferred by syringe to each bag, for a final volume of ~91.1 mL. This process was repeated in quintuplicate, resulting in a total of 20 intravenous bags (Dose 1: n = 5 for NS, n = 5 for D5W; Dose 2: n = 5 for NS, n = 5 for D5W). The contents of each set of 5 intravenous bags were pooled into a particle-free container, and 100 mL of this pooled solution was transferred into the I-Flow Homepump Eclipse and AccuFlo elastomeric infusion devices. The filled pumps were stored at ambient room temperature and at 5°C (± 3°C). Time zero testing was performed on the remaining solution.

Elastomeric infusion pumps

The 2 elastomeric pumps used in this study were the AccuFlo and the I-Flow Homepump Eclipse. These pump models were chosen because each pump can contain approximately 100 mL and can infuse the entire 100 mL over 1 hour.

Testing and sampling time points

The solution hold time was evaluated for 10 days at 5°C (± 3°C) (tolerance ± 3 hours) and for 1 day (24 hours) at ambient room temperature (tolerance ± 3 hours). These hold times were chosen to bracketed concentrations the currently approved intravenous bag hold studies.

Table I
Preparation of solution samples.

Test	Total volume reserved (mL)	Solution preparation (mL)	
		Dose 1	Dose 2
Appearance	40	20*	20*
Particulates (USP 788)	40	20*	20*
Assay	4	1.5 diluted to 50 with diluent	2.5 diluted to 10 with diluent
Related substances	5	3.3 diluted to 10 with diluent	No dilution
pH	10	5*	5*

* No dilution.

Samples from both pump types for all ceftolozane/tazobactam reconstitution/dilution schemes and concentrations were removed through the pump tubing at the 24-hour and 10-day time points. At each time point, a single 20-mL aliquot for each solution was examined for appearance in terms of clarity, color, and visible particulates, according to the US Pharmacopeia⁸ and the European Pharmacopoeia Method⁹ (Table I). At each time point, the subvisible particle count was evaluated. A volume of 20 mL of each sample was evaluated using a light-obscuration particle counter. Each sample was analyzed according to USP.¹⁰ The pH of each ceftolozane/tazobactam sample from both pumps and the PVC bag was also evaluated at each time point using a SevenMulti pH meter (Mettler Toledo, LLC, Columbus, Ohio). No duplicate testing was performed for either the solutions or the time points. The testing was performed at specific intervals defined within the protocol, making the variability of testing low.

Data analysis

Analyses were carried out by qualified analysts at Steri-Pharma, LLC (Syracuse, New York). Chemical stability was defined as the recovery of more than 90% of the initial concentration of ceftolozane/tazobactam.¹¹ For the evaluation of the appearance of the solution, pH, and subvisible particulates, the data were evaluated based on “no significant change” from the initial time point (T0) solution to the hold solutions.

Results

Appearance, subvisible particulate, and pH

At each time point, the visual appearance of all pump and PVC bag solutions remained clear and free of visible particulates. Values obtained through subvisible particulate matter evaluation did not differ significantly between T0 and 10 days (T10) (Table II).

No notable changes in pH were observed in any of the pump or PVC solutions throughout the study from T0 to T10, with a maximum pH range of 5.5 to 6.0 and 5.6 to 6.1 for the 150-mg and 1500-mg doses, respectively (Table II).

Assay

Recovery of ceftolozane and tazobactam was greater than 93% and 94%, respectively, for all samples (elastomeric pump and PVC bag) at 10 days, which was greater than the recovery acceptance rate of 90% (Table II).

Discussion

An increasing number of patients are being treated with intravenous antibiotics in the outpatient setting, and portable

Table II
Elastomeric pump stability of ceftolozane/tazobactam in the elastomeric infusion pumps and in polyvinylchloride bags.

Dose	Temperature	Reconstitution/dilution solution	Sampling time point	Assay [*]		Subvisible particulates		pH	
				Ceftolozane (≥ 90% of T0)	Tazobactam (≥ 90% of T0)	Particulates ≥ 10 μm/mL	Particulates ≥ 25 μm/mL		
I-Flow Homepump Eclipse [†] Dose 1 (150 mg)	5°C	0.9% saline	T0 solution	100	100	4	0	6.0	
			T10 solution	95	98	0	0	5.9	
		5% dextrose	T0 solution	100	100	8	0	6.0	
			T10 solution	98	100	0	0	5.8	
		Ambient room temperature	0.9% saline	T0 solution	100	100	11	0	6.0
			T24 solution	102	104	1	0	5.9	
	Dose 2 (1500 mg)	5°C	0.9% saline	T0 solution	100	100	2	0	5.9
				T10 solution	96	100	0	0	5.9
		5% dextrose	T0 solution	100	100	3	0	5.8	
			T10 solution	98	100	0	0	5.9	
		Ambient room temperature	0.9% saline	T0 solution	100	100	5	0	5.8
			T24 solution	95	96	0	0	5.9	
5% dextrose	T0 solution	100	100	7	0	5.8			
	T24 solution	100	100	0	0	5.9			
AccuFlo [‡] Dose 1 (150 mg)	5°C	0.9% saline	T0 solution	100	100	33	1	6.0	
			T10 solution	99	101	1	0	5.9	
		5% dextrose	T0 solution	100	100	13	0	6.0	
			T10 solution	99	100	0	0	5.8	
		Ambient room temperature	0.9% saline	T0 solution	100	100	33	1	6.0
			T24 solution	99	101	3	0	5.9	
	Dose 2 (1500 mg)	5°C	0.9% saline	T0 solution	100	100	12	0	6.0
				T10 solution	100	100	0	0	6.1
		5% dextrose	T0 solution	100	100	1	0	5.6	
			T10 solution	100	102	0	0	6.0	
		Ambient room temperature	0.9% saline	T0 solution	100	100	12	0	6.0
			T24 solution	97	98	1	0	6.1	
5% dextrose	T0 solution	100	100	1	0	5.6			
	T24 solution	97	98	6	0	5.7			
Polyvinylchloride bag Dose 1 (150 mg)	5°C	0.9% saline	T0 solution	100	100	3	0	5.6	
			T10 solution	101	102	2	0	5.6	
		5% dextrose	T0 solution	100	100	2	0	5.8	
			T10 solution	100	98	2	0	5.5	
		Ambient room temperature	0.9% saline	T0 solution	100	100	1	0	5.7
			T24 solution	99	102	2	0	5.7	
	5% dextrose	T0 solution	100	100	1	0	5.9		
		T24 solution	96	98	2	0	5.7		

T0 = initial time point; T10 = time point out to 10 days; T24 = time point out to 24 hours.

* Assay value is the percentage assay compared with the T0 solution.

[†] Halyard, Alpharetta, Georgia.

[‡] EMED Technologies, El Dorado Hills, California.

elastomeric pumps are widely used because of their ease of operation.⁵ Reconstitution and dilution of ceftolozane/tazobactam in a sterile environment can extend the stability of intravenous medications from 24 hours to 10 days, potentially reducing drug waste and eliminating the need for frequent clinic visits.^{12,13}

The data from this study, together with existing stability data,² demonstrate that ceftolozane/tazobactam remains physically and chemically stable for at least 7 days when reconstituted, diluted, and stored in the I-Flow Homepump Eclipse and AccuFlo elastomeric pumps and in PVC intravenous bags. No significant adsorption or chemical or physical change occurred when ceftolozane/tazobactam in solution (150 mg and 1500 mg) was stored in elastomeric containers for a period of 10 days at 5°C.

Although these results confirm the stability of a 1.5-g dose of ceftolozane/tazobactam in several pump types and in PVC bags, the study had limitations. These results may not be applicable to other pump types, depending on the design of the pump or the elastomeric materials used, or to diluents other than those used

in this study. Additional studies are required to determine the stability of ceftolozane/tazobactam at the higher 3 g q8h dose and associated concentrations under study for nosocomial pneumonia. Finally, this study evaluated only the stability of ceftolozane/tazobactam; no analyses were performed to determine the safety or microbiological efficacy of the stored solutions.

Conclusions

Despite some limitations, the results of our study confirm the physical and chemical stability of ceftolozane/tazobactam for at least 7 days, when reconstituted, diluted, and stored as described, in 2 types of elastomeric pump and in PVC intravenous bags. These data support the potential use of elastomeric pumps for ceftolozane/tazobactam administration in an outpatient setting.

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Conflicts of Interest

Funding for this research was provided by Merck & Co, Inc, Kenilworth, NJ. Dr. J. Terracciano and Dr. E.G. Rhee are employees of Merck & Co, Inc, Kenilworth, NJ. Ms. J. Walsh was an employee of Merck & Co, Inc, at the time the study was performed; she is now an employee of Shire Pharmaceuticals, Lexington, MA. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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