PP-022

EXTENDED STABILITY OF 2.5 mg/mL BORTEZOMIB SOLUTION IN SYRINGES AND OPENED VIALS

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Bortezomib (Velcade®) is indicated for treatment of multiple myeloma and mantle cell lymphoma. Bortezomib is reconstituted with 0.9% sodium chloride (NS) at 1mg/mL for intravenous administration and at 2.5mg/mL for subcutaneous use. The product information states that in-use stability of the reconstituted solution is 8 hours at 25°C in original vial or a syringe. Several studies demonstrated the stability of bortezomib 1mg/mL in NS for up to 5 days. This allows Hospitals to reduce waste and results in significant cost savings. The extended stability for s.c. bortezomib has not been well-supported yet.

OBJECTIVES

To determine the chemical and physical stability of 2.5mg/mL-bortezomib solution in NS stored in polypropylene syringes and opened vials under refrigerated conditions and clinical use conditions.

MATERIALS AND METHODS

Chemical stability was defined as the retention of ≥ 95% of the initial drug concentration (EU approved specification limit for assay of bortezomib (Velcade®)), determined by a validated HPLC method based on a previously reported HPLC method (range: 50-175 µg/mL). Degradation product levels were also measured (quantitation limit ≤ ICH reporting threshold for unidentified degradation products). Physical stability was assessed by visual inspection and dynamic light scattering. Physico-chemical stability was defined as solutions with 4.0-7.0 pH values. Statistical analysis were performed (α=0.05).

RESULTS

More of 95% of the initial concentration of bortezomib remained in the original vials and polypropylene syringes for 7 days at 5±3°C and for 24 h at 25°-30°C (protected from light)(Table 1).
All samples met the acceptance criteria for appearance, physical attributes and pH. At no time, the level of degradation products was greater than the ICH reporting threshold (Table 2).

Table 1. Stability of Bortezomib (2.5 mg/mL) in storage containers (vials and syringes) at 5±3°C and darkness[a]

Sample Type	Initial drug concentration (mg/mL) Mean ± S.D.	Drug concentration remaining (%) Mean ± S.D.				
		1 day	3 days	4 days	7 days	10 days
Glass vial	2.46 ± 0.01	99.75 ± 0.26	97.59 ± 0.54	98.05 ± 0.35	95.89 ± 0.33	91.56 ± 0.60
Polypropylene syringes	2.45 ± 0.04	100.76 ± 0.24	98.02 ± 0.62	97.62 ± 0.68	95.84 ± 0.41	91.02 ± 0.53

Table 2. Impurities of Bortezomib (2.5 mg/mL) in storage containers (vials and syringes) at 5±3°C and darkness[a]

Sample Type	Impurity	Mean ± S.D. % of the drug substance		
		4 days	7 days	10 days
Glass vial	Impurity 1	0.03±0.001	0.04±0.001	0.04±0.002
	Impurity 2	0.01±0.001	0.01±0.001	0.01±0.001
Polypropylene syringes	Impurity 1	0.04±0.001	0.03±0.001	0.03±0.001
	Impurity 2	0.01±0.001	0.01±0.001	0.01±0.001

[a]All data are mean ± S.D. of test results for all analyzed samples (n=2) of each preparation.

Figure 1. Chromatograms of bortezomib reference solution (125 µg/mL) (A) and bortezomib test solution (125 µg/mL) at 10 days under 5±3°C and darkness (syringe) (B)

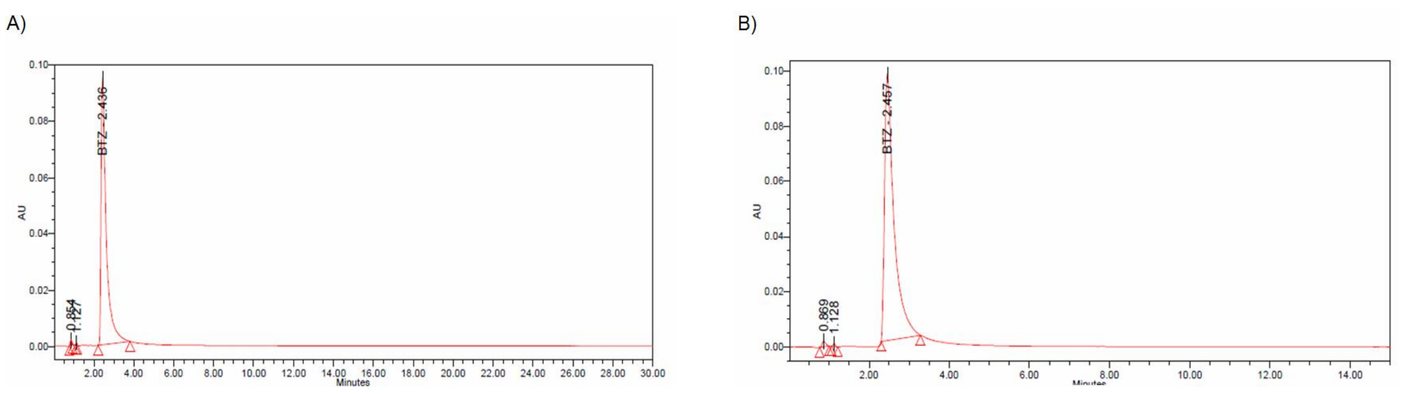
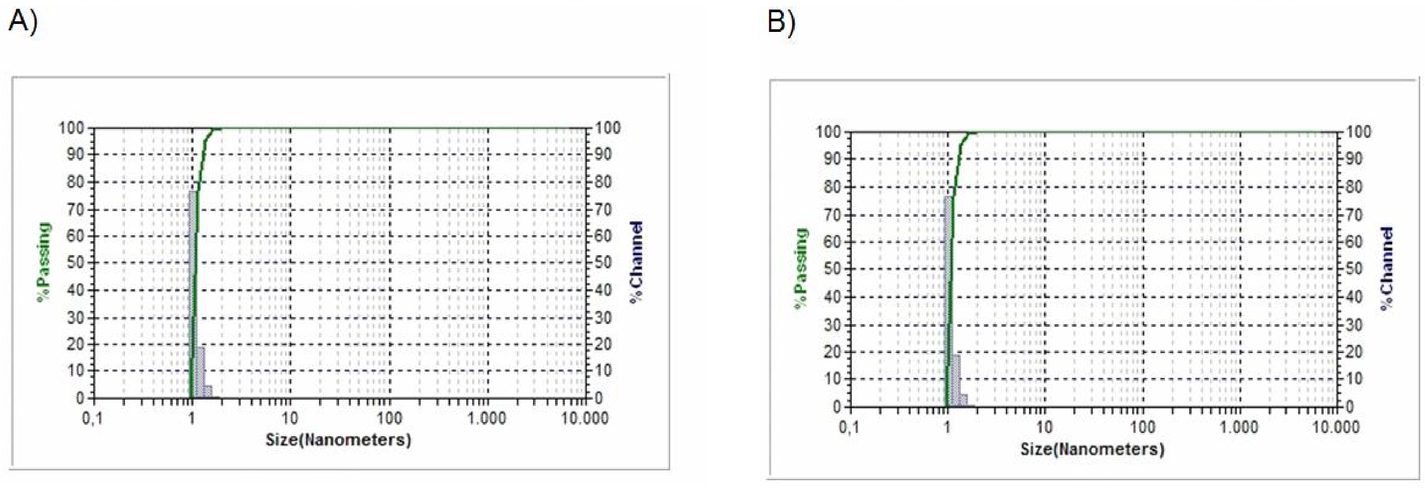


Figure 2. Particle size-Histograms of s.c. bortezomib solution (2.5 mg/mL, vial) at time zero (A) and at 10 days under refrigerated conditions (5±3°C and darkness) (B)



CONCLUSIONS

Bortezomib 2.5 mg/mL in NS is stable for 7 days at 5±3°C and for 24 hours at 20-30°C, when stored in both polypropylene syringes and vials (protected from light).