CHEMICAL STABILITY OF BORTEZOMIB SOLUTIONS IN ORIGINAL MANUFACTURER VIALS

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INTRODUCTION

Bortezomib is a drug used in the treatment of mieloma multiple. The experiments carried out demonstrate that bortezomib is cytotoxic for different types of neoplastic cells and reduces the tumor-like growth "in vivo" in many preclinical models of tumor, including myeloma multiple.

As an alternative to intravenous delivery, subcutaneous administration of bortezomib could be a good option for patients, particularly those with poor venous access. Subcutaneous administration eliminates the need for repeated intravenous access or insertion of long-term central venous access devices, improving convenience for patients and physicians. Subcutaneous administration is used for several antineoplastic agents that are not directly toxic to tissues, such as alemtuzumab. Intravenous injection is the standard administration route of bortezomib; however, subcutaneous administration is an important alternative.

In a recent study, was evaluated the effectiveness and security of the subcutaneous administration of bortezomib as opposed to the conventional intravenous administration. It is necessary to emphasize that the concentration of the solution used for subcutaneous administration is 2.5 mg/ml, unlike the dissolution for intravenous injection is prepared to 1 mg mL^{-1}

OBJECTIVE

The objective of this work was to evaluate the stability of bortezomib reconstituted with sterile NaCl 0.9% to a concentration of 2.5 mg mL^{-1} in original manufacturer vial refrigerated at 4 ºC in the dark.

METHOD

Instrumentation

HPLC analysis was performed at room temperature (~25ºC) using a Shimadzu LC-6A pump equipped with Rheodine 7125 injection valve 20 µL, a Shimadzu SPD-6A spectrophotometric detector working at 270 nm. The signal from the detector was recorder and integrated with a chromatography data system Shimadzu C-R6A chromatopac; a LiChrospher® 100 C18 (5 µm) LiChroCART® 250-4 column was employed. The mobile phase consisted of acetonitrile:water (40:60, v/v).
Flow rate: 1.5 mL min^{-1}. Retention time: 3.5 min

Materials

Bortezomib is commercialized by Millennium Pharmaceuticals (Mass, USA) in the US and Janssen-Cilag in Europe under the trade name Velcade. The vials are reconstituted with 1.4 mL of sterile NaCl 0.9% to obtain 2.5 mg mL^{-1} solution of bortezomib. The product information states that reconstituted bortezomib at 1.0 mg mL^{-1} is stable for 8 hours when stored at <25ºC and protected from light, and for 3 hours in a syringe. No information was available at this moment about the stability of bortezomib solution at 2.5 mg mL^{-1} concentration.

RESULTS AND DISCUSSION

Physical stability

All solutions, as reconstituted in the original manufacturer's glass vials, were initially clear and colourless and remained so for the duration of the study. Also, no visible particles were observed in any solution throughout the study period.

Accelerated degradation analysis

pH study

The ultraviolet spectrum of bortezomib (200-365 nm) shows no variation in acid, neutral and basic medium with a maximum wavelength at 270 nm in all cases. Chromatograms of the samples in acidic, basic and neutral medium at different concentrations let to obtain a calibration graphs with a similar slopes. The higher difference observed in these chromatograms were the presence of diverse peaks corresponding to a degradation products, principally in basic medium (t_R=2.1 min).

Heat study

A sample of 125 ppm of bortezomib was heat at 90ºC during different times. In the chromatogram of bortezomib obtained after heat the sample appears clearly the same degradation product mentioned above as can be seen in figure 1. The results obtained were shown in figure 2.

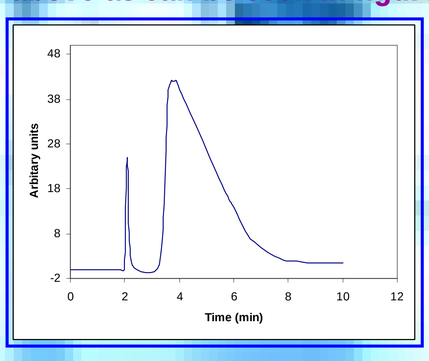

Figure 1. Chromatogram obtained after heat the sample

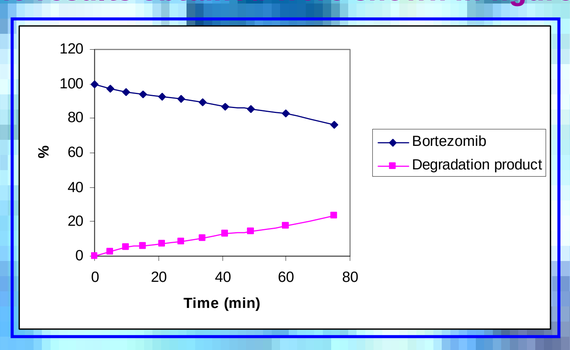

Figure 2. Percentage remains of bortezomib and the degradation product after heat

Bortezomib analysis

Table 1 provides stability data of bortezomib (2.5 mg mL^{-1}) stored at 4ºC in the dark over 30 days, tested at a diluted concentration of 125 µg mL^{-1}.

Table 1

Study day	Concentration of bortezomib (mean ± SD, µg mL^{-1})	(Percent of bortezomib remaining)
Day 0	122.38 ± 0.99	97.90
Day 1	110.23 ± 1.24	88.18
Day 2	120.13 ± 0.84	96.10
Day 3	116.16 ± 0.80	92.93
Day 4	111.11 ± 2.21	88.89
Day 7	119.49 ± 2.05	95.59
Day 9	118.50 ± 1.89	94.80
Day 14	118. 00 ± 2.10	94.40
Day 22	117.94 ± 2.25	94.35
Day 30	122.68 ± 1. 15	98.14

Influence of hydrogen peroxide

Degradation of bortezomib with hydrogen peroxide occurs quickly. At ambient temperature, 0.2 mL of 125 µg mL^{-1} of bortezomib solution was degraded completely when 50 µL of hydrogen peroxide solution (30%, 3% or 0.3 %) were added and the degradation product appears to 4.7 min. Solutions with lower concentration of hydrogen peroxide degrade bortezomib more slowly, as can be seen in figure 3.

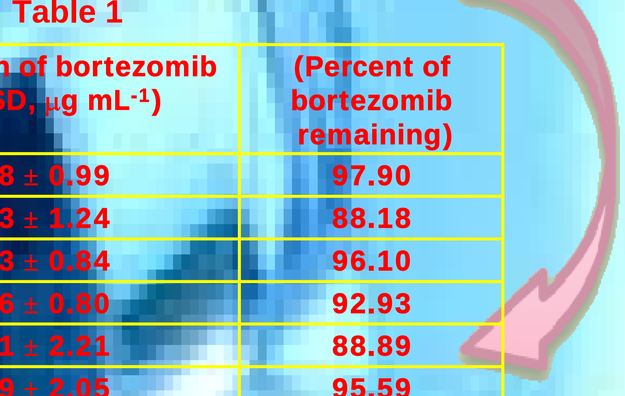

Figure 3. Influence of H_2O_2 (A: 300 µL (50 ppm) + 20 µL 0.03 % H_2O_2)); B: (200 µL (125 ppm) + 50 µL 0.03 % H_2O_2)); C: (300 µL (125 ppm) + 100 µL 0.03 % H_2O_2))

Influence of sodium hypochlorite

Degradation of bortezomib with sodium hypochlorite also occurs quickly. At ambient temperature, 0.7 mL of 125 µg mL^{-1} of bortezomib solution was degraded completely when 50 µL of sodium hypochlorite solution 0.02 M was added and degradation product appears at 5 min when the sample is chromatographied immediately. After 10 min, this degradation product was newly degraded in other products (t_R= 2.1, 3, 3.2, 8.1 min). After 30 min from the addition of sodium hypochlorite solution, new degradation products appear between 3 and 4 min in the chromatogram without resolved. The addition of 50 µL of sodium hypochlorite solution 0.002 M to 0.8 mL of 125 ppm of sample produced an immediate degradation, until 29% approximately and this percentage stays constant almost up to 45 min.

CONCLUSIONS

Subcutaneous administration is an important alternative to intravenous injection but the necessary concentration in this case is 2.5 mg mL^{-1}. The stability of these solutions have not been studied at this moment. In this work, we have investigated the stability at this concentration (2.5 mg mL^{-1}).
Reconstituted bortezomib 2.5 mg mL^{-1} was physically and chemically stable at 4 ºC in the dark at least for 30 days in the original manufacturer vial.