CHEMICAL STABILITY OF BORTEZOMIB SOLUTIONS IN ORIGINAL MANUFACTURER VIALS

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INTRODUCTION

Bortezomib is a drug used in the treatment of multiple myeloma. 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 neoplastic cells and reduces the tumor-like growth “in vivo” in many preclinical models of tumor, including myeloma multiple.

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\(^{-1}\) to a concentration of 2.5 mg mL\(^{-1}\). The stability of these solutions have not been studied at this concentration in this case is 2.5 mg mL\(^{-1}\).

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

\textbf{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 are the presence of diverse peaks corresponding to a degradation products, principally in basic medium (t\(_{R}=2.1\) min).

\textbf{Heat study}

A sample of 125 ppm of bortezomib was heated at 90°C 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 are shown in figure 2.

Bortezomib analysis

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

\begin{table}[h!]
\centering
\begin{tabular}{|c|c|c|}
\hline
Study & Concentration of bortezomib & (Percent of bortezomib remaining) \\
\hline
Day 0 & 117.48 ± 0.99 & 97.90 \%
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Day 1 & 114.17 ± 0.74 & 94.18 \%
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Day 2 & 111.62 ± 0.84 & 91.66 \%
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Day 3 & 109.08 ± 0.44 & 89.89 \%
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Day 4 & 106.49 ± 0.12 & 88.35 \%
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Day 7 & 105.05 ± 0.65 & 95.59 \%
 \hline
Day 9 & 104.06 ± 1.09 & 94.98 \%
 \hline
Day 12 & 104.06 ± 0.10 & 94.48 \%
 \hline
Day 22 & 117.48 ± 1.15 & 97.98 \%
 \hline
\end{tabular}
\caption{Table 1}
\end{table}

\textbf{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 (100, 160 or 0.3 %) were added and the degradation product appears at 4.7 min. Solutions with lower concentration of hydrogen peroxide degrade bortezomib more slowly, as can be seen in figure 3.

\textbf{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 chromatographed immediately. 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 0.02 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°C in the dark for 30 days in the original manufacturer vial.