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Freeze-dried kit formulation of 177Lu- and 90Y-labeled immunoconjugates of Trastuzumab – formulation and characterization

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Trastuzumab is a monoclonal antibody for treatment of HER2 positive breast cancer. Immunoconjugate of this antibody labeled with lutetium-177 and yttrium-90 has been investigated as potential radiopharmaceutical for radioimmunotherapy. In our study, the labeling was done via DOTA, DTPA and 1B4M-DTPA as a chelator in a molar ratio of 1:20.
Material and Methods: Several techniques have been used to characterize the stability and retained immunoreactivity of the antibody in the formulated immunoconjugates. A protein integrity and purity were accessed by Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE). Vibrational (infrared and Raman) spectroscopy provided molecular structure information and was found convenient for verification of possible changes in the secondary structure. The number of chelating groups per one trastuzumab molecule was obtained by MALDI-TOF-MS. After conjugation, the freeze-drying process was performed to obtain stable immunoconjugates for further labeling. Quality control and stability were examined by ITLC using a three different mobile phases (0.9% saline solution, 0.4 M methanol:sodium acetate (1:1) and 0.1M acetic buffer).
Results: The same intensity of the fragments (25 kDa for light chain and 50 kDa for heavy chain) of lyophilized immunoconjugates and pure trastuzumab indicated that there is no degradation of the antibody. The presence of characteristic amide bands in infrared spectra (amide I (1700-1600 cm-1), amide II (1480-1575 cm-1) and amide III bands (1255-1244 cm-1) and Raman spectra (amide I band at ˜1670 cm-1 and amide III band at 1230-1300 cm-1) have also indicated that all samples have retained native secondary structure. An average of 3.92 p-SCN-Bn-DTPA, 3.69 p-SCN-Bn-DOTA and 4.43 1B4M-DTPA groups could be randomly conjugated to an antibody molecule, which represent promising result for successful labeling.
After labeling with 177Lu and 90Y (specific activity of 200 μCi/mL), radiochemical purity and stability studies were performed using ITLC method in 0.9% NaCl and 0.4 M methanol:sodium acetate (1:1) as an appropriate mobile phase. The stability studies after 72 h have revealed that 177Lu-labeled trastuzumab is more stable (< 10% of the released 177Lu) than 90Y-labeled one (< 25% of released 90Y).
Conclusion: Our study shows successful formulation of stable radioimmunoconjugates which makes this proposed freeze-dried kit as potential radiopharmaceutical in vivo investigations.

Key words: Trastuzumab, Bifunctional Chelators, Radiolabeling, Lutetium-177, Yttrium-90.

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