عنوان مقاله:

A new and simple non-chromatographic method for isolation of drug/linker constructs: vc-MMAE evaluation

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Introduction: Auristatin and its derivatives (synthetic analogues of dolastatin ۱۰, an antineoplastic natural product), are highly potent antimitotic agents which have attracted considerable attention because of their cytotoxic activity when targeting tumor cells in the form of antibody-drug conjugates (ADCs). Some sophisticated and expensive equipment such as HPLC are needed for drug/linker isolation. The aim of this study was to provide a simple aqueous work-up procedure for the isolation of such drug/linker constructs. The anti-tumor activity of the extracted drug/linker was also investigated against SKBR۳ and HEK۲۹۳ cancer cell lines, and cell viability was assessed.Methods: In the present study, monomethyl auristatin E (MMAE), a derivative of the cytotoxic tubulin modifier auristatin E, was covalently coupled to maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-vc-PAB), a cathepsin-B-cleavable linker, to obtain MC-vc-PAB-MMAE (vc-MMAE). Afterwards, a non-chromatographic isolation procedure was developed to isolate the drug/linker (vc-MMAE) construct. Silica gel thin-layer chromatography and electrospray ionization mass spectrometry were used to monitor the isolation procedure and to confirm the coupling of the linker to the drug, respectively. Further, the anti-tumor activity of the extracted drug/linker was investigated against SKBR۳ and HEK۲۹۳ cancer cell lines, and cell viability was assessed.Results: After coupling, the isolation process was confirmed as a single spot on the TLC plate. The isolation yield was calculated to be ۶۵%. [M + H]+, [M + ۲Na]+ and [M + ACN + ۲H]+ species were observed in the mass spectra, showing that the coupling of MMAE to the linker is not adversely affected by the workup method. Our data revealed that the isolated vc-MMAE was highly potent against tumor cell lines, exhibiting that the workup procedure did not affect MMAE-mediated cytotoxicity.Conclusion: The isolation method described in this study can be applied for the development of a wide variety of ADCs.

کلمات کلیدی: