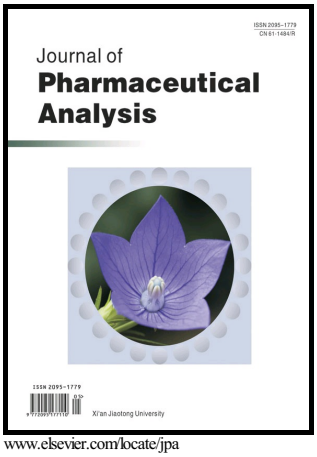

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Use of the Chromatoprobe as a sample sparing technique for residual solvent analysis of drug discovery candidates by gas chromatography

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Abstract

In drug discovery research, residual solvent measurement is an integral part of purity analysis for a synthesis lot of a drug candidate before it is used for toxicity testing. This is usually carried out using gas chromatography with direct injection sample introduction. This method requires testing compounds to verify solubility at high concentrations (>50 mg/ml, usually in DMSO) to achieve acceptable sensitivity, a hurdle which is not always achievable for some samples such as cyclic peptides and oligonucleotides. To overcome the limitation associated with the direct injection approach, a new method using the Chromatoprobe thermal extraction device was developed for quantifying residual solvents of drug discovery compounds. This method not only consumes significantly less material (less than 1 mg), but also shows higher sensitivity, compared to the direct injection approach. In addition, because no diluent is required with the Chromatoprobe thermal extraction, all residual solvents can be detected and measured with no further method optimization. In our study, we compared data from GC residual solvent analysis using the Chromatoprobe solid sample introduction to those of the direct injection method for seven in house samples. Our results showed a good agreement between the data from these two sample introduction methods. Thus, the Chromatoprobe sample introduction method provided a sample-sparing alternative to the direct injection method for the measurement of residual solvents in drug discovery. This method can be particularly useful for residual solvent analysis in samples that are available only in limited amounts, poorly soluble, and/or unstable in the diluents used for the direct injection method.

Keywords: Chromatoprobe, Thermal Extraction, Gas Chromatography, Residual Solvent, Drug Discovery

1. Introduction