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日本薬局方における定量 NMR (qNMR) の利用に関する準備研究 (第 1 報)

細江 潤子[*1], 杉本 直樹[*1], 末松 孝子[*2], 山田 裕子[*3], 三浦 亨[*3], 早川 昌子[*4], 鈴木 裕樹[*4], 勝原 孝雄[*5], 西村 浩昭[*5], 菊地 祐一[*5], 山下 忠俊[*6], 合田 幸広[*1,#]

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Preliminary Studies for Application of Quantitative NMR (qNMR) in the Japanese Pharmacopoeia (I)

Junko HOSOE[*1], Naoki SUGIMOTO[*1], Takako SUEMATSU[*2], Yuko YAMADA[*3], Toru MIURA[*3], Masako HAYAKAWA[*4], Hiroki SUZUKI[*4], Takao KATSUHARA[*5], Hiroaki NISHIMURA[*5], Yuuichi KIKUCHI[*5], Tadatoshi YAMASHITA[*6] and Yukihiro GODA[*1,#]

Summary

Preliminary studies were performed to establish the quantitative nuclear magnetic resonance ("qNMR) test" in the crude drug test section of the Japanese Pharmacopoeia (JP). In this report, we examined impurity signals from internal reference substances and targeted marker compounds, chemical shifts of internal reference substances, and the suitability of signal peaks of targeted marker compounds for qNMR.

For example, the internal reference substance 1,4-BTMSB-d_4 showed an impurity signal at about 7.3ppm derived from 1,4-$(Me_3Si)_2$-$C_6D_3\underline{H}$ in the highly accumulated NMR spectrum at 400 MHz. The impurity signal increased time-dependently in $CDCl_3$, but not in CD_3OD or CD_3COCD_3. This impurity signal interfered with integration of the signal of geniposide at 7.26ppm. Therefore, we consider that this signal of geniposide is unsuitable for quantification. Our data also suggest that it is important to measure qNMR immediately after sample preparation when $CDCl_3$ is used as the solvent. Similarly, the highly accumulated NMR spectrum of another internal reference substance, DSS-d_6, showed impurity signals at 0.59, 1.72 and 2.88ppm in D_2O and at 0.48, 1.54 and 2.37ppm in DMSO-d_6, which are derived from $Me_3SiC\underline{H}DCD_2CD_2SO_3Na$, $Me_3SiCD_2C\underline{H}DCD_2SO_3Na$, and $Me_3SiCD_2CD_2C\underline{H}DSO_3Na$, respectively. Therefore, it is considered essential that the spectral regions around these impurity signals be avoided in selecting suitable signals of targeted compounds for integration. Very small, but distinct, impurity signals also appeared in the spectra of several targeted marker compounds when the data were obtained under highly accumulated (about 3800 times) conditions. These observations suggest that prior determination of impurity signals arising from the internal reference substances and the targeted samples would be essential to assure the validity of qNMR.

The present results are expected to be helpful in the process of establishing " the qNMR test" in the JP.

Key words

Quantitative NMR, Impurity signals, Japanese Pharmacopoeia, 1,4-BTMSB-d_4, DSS-d_6, Marker compounds