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Nuclear Magnetic Resonance: Its Utility and Reliability in the Analysis of Pharmaceutical Active Agents/Metabolites in Biological Fluids

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Editorial

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Abstract

Isothiazoles are the significant topics of heterocyclic compounds as the heterocyclic system is one of the most important building blocks for new materials possessing interesting electronic, mechanical or biological properties. The isothiazoles also find vast application to search for the alternative synthetic strategies and development of novel molecular structures. The most recent findings in the fields of isothiazoles are described here in a systematic way. Some of the important applications in the pharmaceutical fields are also studied and reported here in this review study. It is desirable that the chemists get the value up to date information from this report regarding the synthesis, reactions and pharmaceutical importance of isothiazoles.

Keywords: Isothiazoles; Pharmaceutical Importance; Synthesis; Medicinal importance

Abbreviations: NMR: Nuclear magnetic resonance; CSF: Cerebrospinal Fluid.

Editorial

Nuclear magnetic resonance (NMR) is a spectroscopic analytical technique involving absorption of electromagnetic radiation in the radio-frequency region of the spectrum giving rise to resonance signals emitted by the various atomic nuclei present in the chemical compound (sample). It takes advantage of the magnetic properties of many nuclei such as IH, l3C, 19F and 31P. In analytical works, proton NMR (1H-NMR) and carbon NMR (13-C NMR) are mostly used. Proton-NMR has advantage over other forms of NMR spectroscopy due to the ubiquity of the proton in chemical structure. Carbon NMR, despite some practical problems (relaxation time, filter characteristics, power level of the exciting pulse, dynamic range, digital resolution) associated with it, a large chemical shift range as well as the sensitivity of its chemical shifts to small differences in molecular environment have given 13C-NMR greater potential than 1H-NMR for the study of organic chemical compounds and analyzing complex mixtures [1].

In 13-C-NMR, it is preferable to add a relaxation reagent to eliminate saturation related to relaxation times that alter the intensity of the signal. Both 1H-NMR and 13-C NMR have been used to identify and quantify drugs/metabolites in biological fluids. Analysis with1H-NMR is generally performed using NMR spectrophotometer of either moderate field strength

(250-300 MHz) or higher field strength (400-600 MHz). Internal standard method or standard addition method is the preferred method in sample quantification. The NMR spectra generated are plots of signal intensity against frequency. The chemical shifts (positions of signals) on the NMR spectrum are used in the identification of drugs/metabolites while peak areas or peak heights of the signals are utilized to quantify their concentrations [2]. Chemical shift is a phenomenon that explains how the variation in shielding constant (δ) affect the resonant frequency of atomic nucleus and is obtained by measuring the frequency difference between the signal of a chemical compound (analyte) and that of internal standard [3]. The internal standard serves as a reference as well as the frequency of the instrument imposed by design. In the present article, the qualities that make nuclear magnetic resonance spectroscopy a reliable technique to be utilized in the analysis of drugs/metabolites in biological fluids were considered as well as those drugs/metabolites analyzed by the technique. Biological fluids (intracellular and extracellular) are very vital to life and help maintain body homeostasis. The biological fluids of interest in this paper are extracellular fluids namely blood (whole blood, serum or plasma); urine; cerebrospinal fluid (CSF); amniotic fluid; ocular fluid; pleural fluid (from the sac surrounding the lungs); pericardial fluid (from the sac surrounding the heart); peritoneal fluid (also called ascitic fluid; from the abdomen); saliva and synovial fluid (fluid that is found in joint cavities). Any of these fluids could be analyzed for parent drugs/metabolites however blood and urine are mostly the fluids of choice. Some of the qualities of NMR spectroscopy that attract analytical chemists in utilizing the technique in preference to other instrumental analytical methods to determine drugs/metabolites in biological fluids include

- Reduction in pre-analytical preparation time and the potential to detect and quantify drugs and metabolites simultaneously.
- Resolving metabolites of very similar molecular structure.
- Use of small sample volume and rapid analysis.
- Straight forward quantification.
- Sample is not destroyed.
- The lack of absorbing chromophores for ultraviolet–visible detection.
- The need for the special chromatographic detectors.
- Difficulties in establishing highly efficient solid or liquid phase extraction procedures.
- Results could potentially be provided within 30 min of analysis.
- In terms of calibration, the spectra can be calibrated by internal standard method, standard addition method or external method. Standard addition method is the most reliable approach as it reduces matrix effects such as ionic strength, pH or viscosity.
- In terms of linearity, peak areas or peak heights are a direct reflection of the number of hydrogen atoms (IH-NMR) or carbon atoms (13C-NMR) in a given magnetic environment. For a homogeneous solution, the technique is theoretically linear over several orders concentrations.
- In terms of quantification, NMR spectroscopy can be a precise and accurate analytical technique, however, poor signal to noise ratios, and areas of bad phasing in complex mixtures contribute to inaccuracy.
- In terms of sensitivity, NMR as a Fourier transform interfaced technique can increase the signal to noise ratio in the spectra by increasing the number of scans employed to collect the data set.

Regarding its reliability as analytical method in the determination of drugs/metabolites in biological fluids, nuclear magnetic resonance spectroscopy has been utilized to identify and quantify acetaminophen [4], ibuprofen, aspirin, valproate [5], diethyl carbamazepine [6], pseudoephedrine, chloroquine [7] and other pharmaceutical active agents [8]. Such biological fluids studied include but not limited to amniotic fluid [9,10], bile [11], cerebrospinal fluid [12,13], plasma [14-16], synovial fluid [17,18] and urine [19].

Identification was made possible because these drugs/metabolites have several characteristic multiplet resonances that are resolved from the peaks of endogenous metabolites and matched to the characteristic peaks spectra of the standard drugs. However, in some cases, presence of analyte was confirmed by spiking the specimen with reference standard compound, then re-acquiring the spectrum, or by spin-decoupling experiments. Quantification was achieved because signal areas can be generated as numerical values proportional to the area or from the integration plots that are superimposed on the spectrum.

Conclusion

The study has shown that 1H-NMR was mostly used in the analysis of drugs/metabolites in biological fluids probably because a useful NMR spectrum can be obtained very quickly (5 minutes) with low concentration of analyte solution, in contrast to 13C-NMR that normally requires longer scan time (~20-30 minutes) and a more

concentrated analyte solution. The use of two-dimensional NMR can improve the effective spectral resolution and facilitate the identification and quantification of drugs/ metabolites. A higher detection limit of NMR could be significantly lowered by the use hyphenated system (NMR-MS) thus allowing NMR to probe even lower concentrated drugs/metabolites, or HPLC-NMR-MS to enhance the capabilities of NMR in metabolite profiling. Finally, the use of a high-field instrument makes nuclear magnetic resonance spectroscopy a reliable technique to be utilized in the analysis of pharmaceutical active agents/metabolites in biological fluids because spectral quality would be improved by reducing overlap with endogenous metabolites, complex spectral patterns would be simplified, and drugs/metabolites would be detected at lower levels by improving analytical sensitivity.

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