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APEIE – 2018

ТРУДЫ XIV МЕЖДУНАРОДНОЙ НАУЧНО-ТЕХНИЧЕСКОЙ КОНФЕРЕНЦИИ АКТУАЛЬНЫЕ ПРОБЛЕМЫ ЭЛЕКТРОННОГО ПРИБОРОСТРОЕНИЯ

АПЭП – 2018

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Том 1

Часть 1

Новосибирск, 2-6 октября, 2018

Using a spectrometer «Kazan-Nova II» to identify drugs by nuclear quadrupole resonance

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Abstract – **The hardware-software complex based on the home-build nuclear magnetic/quadrupole resonance spectrometer "Kazan-Nova II", which allows to determine the authenticity of nitrogen-containing drugs by a nondestructive method is considered in the article. The possibility to distinguish the drugs from different manufacturers using their NQR spectra is shown, which makes it possible to use this device as a scanner of the authenticity of medicinal products, as well as for the formation of a database of reference spectra.**

Keywords – **Nuclear Quadrupole Resonance, the quality of medicines, non-destructive testing, sensitization.**

I. INTRODUCTION

ACCORDING to the official statistics of the World Health Organization (WHO), the market of counterfeit (fake, counterfeit) medicines reaches 30 billion dollars. According to official data in Russia counterfeit medicines are 2-4% of market, but according to unofficial data the amount of counterfeit drugs is much higher and in some positions reaches 10%. In Europe, the percentage of substandard medicines is lower than in Russia, in countries of Asia and Africa, the proportion of counterfeit medicines reaches 50% [1 - 5]. Official laboratories under the supervision of Federal Service on Surveillance in Healthcare are constantly monitoring the quality of medical products, but their capabilities make it possible to verify only 1% of medicines on the market. Therefore, in recent years, state decisions have been made to strengthen the quality control of Medical Products (MP) and methods for the diagnosis of medicinal products are actively developing. To date, laboratories that control the quality of drugs are equipped with modern analytical instruments. A mandatory set are usually the methods of chemical analysis, chromatographic analysis, IR spectroscopy, mass spectroscopy. Most of these methods of research allow for a qualitative analysis of MP for compliance with regulatory documents. However, the existing analytical equipment has a number of shortcomings. For example, preliminary preparation of a sample is required to make a test sample. The equipment is often cumbersome and requires qualified personnel. Modern analytical method based on Raman spectroscopy (scattering) deprived of the major drawbacks - is provided nondestructive testing, i.e., you can analyze without damaging the package, and the scanners are portable and easy to operate [6, 7]. At the same time, their use is limited by the requirements of optical transparency of the medium, which means that it is impossible to study MP in opaque packages, most tablets and powders in capsules. Therefore, the nuclear quadrupole resonance (NQR) technique has prospects as an additional method for determining the quality of MP, since it allows us to investigate the chemical compounds in the solid phase directly in the package (in blisters, plastic and carton boxes and tubes). It is also important that it is possible to create a portable spectrometer.

II. PROBLEM STATEMENT

The application of the nuclear quadrupole resonance method is a relatively "fresh" method for testing the quality and authenticity of medicinal products. The main work in this field began in the UK after the 2000s and quite logically grew out of studies devoted to methods of detecting and searching for explosive and narcotic substances using the NMR / NQR method [8-10]. One of the problems of NQR is the rather low sensitivity of the method, which is a weak signal-to-noise ratio, which is especially characteristic for nitrogen-containing substances. The amplitude of the NQR signal is usually proportional to the resonant frequency, and since for N-14 nitrogen the frequencies are in the range 0.6-6 MHz, efforts are required to ensure a reliable recording of the NQR spectra. In recent years, by several research teams, the main problems of the low sensitivity of NQR in detecting explosive compounds have been successfully solved. There are prototypes of baggage scanners, mines detectors and explosives hidden under clothing. Progress was achieved through solving a wide range of problems: new equipment and sensors, specially selected multi-pulse series and protocols of exciting pulses, methods of mathematical signal processing and noise reduction, etc. For NQR spectroscopy of drugs, in contrast to detecting explosives, that the percentage of the active substance is from a few milligrams to grams, which requires further sensitization. Another problem is the need to have "fingerprints" - the reference spectra of the MPs for comparison. Currently, there is a constantly growing database of spectral characteristics, containing more than 100 products of various manufacturers and brands. The hardware-software system based on the home-built NQR spectrometer allows recording the reference spectra of new types (producers) of MPs, supplementing the existing database.

III. BASICS OF THEORY AND EQUIPMENT

A. Basics of nuclear quadrupole resonance

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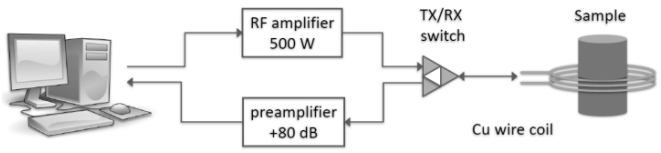
The phenomenon of nuclear quadrupole resonance (NQR) consists in the resonant absorption of electromagnetic energy in crystals, caused by transitions between the energy levels formed as a result of the interaction of the electric quadrupole moment of the nucleus with the electric-field gradient (EFG) at the location of the nucleus. The interaction of the quadrupole moment of the Q nucleus with the electric-field gradient of the crystal qαβ leads to the appearance of energy states corresponding to different orientations of the nuclear spin $\vec{I}$ relative to the crystallographic axes. The radio-frequency magnetic field, like in the case of NMR, causes forced transitions between these states, which is detected as a resonant absorption of electromagnetic energy. Unlike nuclear magnetic resonance (NMR), an external magnetic field is not required to observe NQR, which greatly simplifies the equipment [11]. NQR is observed in a solid aggregate state (mono- and polycrystalline substances), as well as in frozen liquids. Typical nuclei on which NQR is observed are 35Cl, 37Cl, 79Br, 81Br, 127I, 121Sb, 123Sb, 75As, 63Cu, 65Cu, 14N, 10B, 11B, *etc*. NQR is an identifying method, since to each compound there corresponds its own unique spectrum of the investigated nucleus. The main parameters are the resonance frequency, the quadrupole interaction constant, the asymmetry parameter, the relaxation characteristics, the width and shape of the line.

Parameters of the nuclear quadrupole resonance spectrum for each chemical compound are unique. The values of the quadrupole resonance frequencies even for the same nucleus vary significantly in different compounds. Such changes occur as a result of the difference in the magnitude of the electric-field gradient (EFG). EFG on the core is determined by a set of different contributions: the electric charges of neighboring ions, the multipole contributions of the surrounding atomic groups, the electrons of the atom under investigation.

The method of nuclear quadrupole resonance is used to study ferroelectrics, semiconductors, which are used as solar batteries, optical storage devices; superconductors, detection of explosive and narcotic substances, control of pharmaceutical substances, as well as fundamental research in the field of molecular and ionic crystals.

B. Principles of the action of NQR spectrometers

Schematically, the principle of detecting NQR signals is shown in Fig.1.



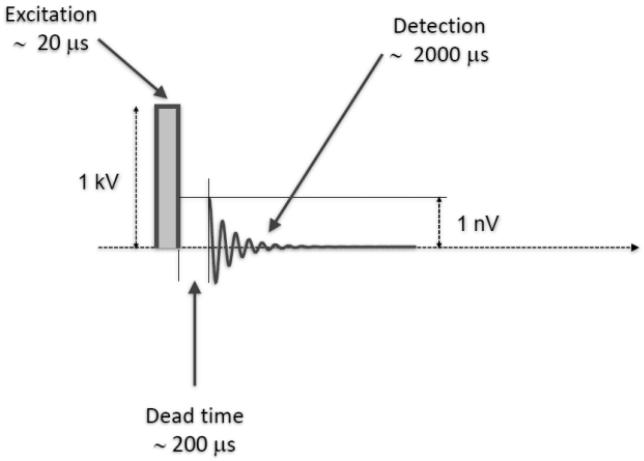


Fig.1 Principle of the action of NQR spectrometer.

The operator specifies the necessary parameters of the pulse sequence: the excitation frequency, the pulse duration and the period of their repetition, the type of the data record. The pulse programmer generates the necessary multi-pulse sequence. Most of the sequences are modified sequences from NMR, although there are also specially developed for NQR. The standard nuclear quadrupole resonance pulse spectrometer contains the following units: a sensor unit, which is a radio frequency coil with a capacitor bank for tuning and matching; radio frequency pulse programmer, generating the necessary sequence of pulses, power amplifier, receiver. The spectrometer is controlled through specialized software installed on a personal computer connected to the spectrometer via the USB interface.

A. NQR techniques for determining the authenticity of medicines.

A significant number of medicinal products contain quadrupole nuclei, for example, NQR can observe spectra of crystals containing nitrogen, chlorine, boron, aluminum, etc. (see Fig.2.).

The most suitable element is nitrogen ^{14}N. Nuclei are part of a large number of drugs. The most popular and therefore most often forged are paracetamol, furasemide, carbazamine, sulfamycil and others. According to research, scientists from the University of King's College London, you can identify several groups of drugs suitable for research by the NQR method [8]. This is a group of MP containing paracetamol, a group of antimalarial MPs, a group of anti-cancer MPs. In addition to MP, food additives can also be studied. Since the NQR frequency is determined by the interaction of the nucleus with the components of the EFG tensor, the spectrum will be unique for each chemical compound. Thus, even for paracetamol, it is possible to differentiate between the preparations of different manufacturers and different forms - in tablets, in powders. Moreover, since the amplitude of the NQR signal is proportional to the number of resonant nuclei, the NQR technique allows not only qualitative but also quantitative control (the percentage of the active substance) to be

produced.

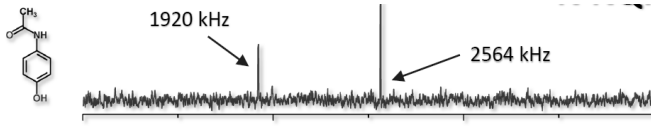


Fig.2. Structure of the paracetamol molecule and resonant frequencies.

IV. SPECTROMETER KAZAN-NOVA II

Modern nuclear magnetic resonance spectrometers are very complex instruments capable of performing a wide variety of experiments. In the last decade, the development of digital electronics has reduced the size and cost of NMR / NQR spectrometers. It should be pointed out that in principle the equipment for NMR and NQR differs only in the presence of a magnet to create a constant magnetic field in the case of observing nuclear magnetic resonance signals. Therefore, in the future, NMR / NQR will appear in the description of the spectrometer. Of course, in the case of NQR, there are special features in the construction of sensors, especially for two- and three-frequency experiments, but this feature is beyond the scope of this article. At the same time, signal processing capabilities and experimental capabilities have significantly expanded. The use of field-programmable gate array (FPGA) made it possible to develop almost completely a digital NMR / NQR spectrometer "Kazan-Nova II" [12].

Kazan-NOVA II is a highly integrated NMR / NQR spectrometer based on FPGA. Scheme connecting the spectrometer to external units is shown in Fig.3. Inside the FPGA, several digital modules are implemented, including a digital part of the frequency synthesizers, a pulse sequencer, a digital quadrature receiver, and a computer interface.

The system is built on a single PCB with a size of 110x180 mm, which implements direct digital synthesis (DDS) schemes for radio frequency (RF) signals, RF pulse generators, signal amplification and detection, filtering, etc. The only two external devices necessary to obtain a full-fledged NQR spectrometer are a low-noise preamplifier and a power amplifier for RF pulses.

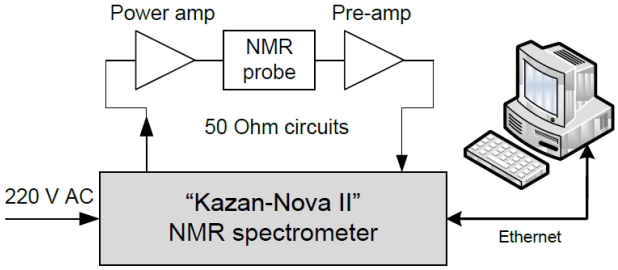


Fig.3. The connection scheme of the "Kazan-Nova II" spectrometer.

The spectrometer has the following characteristics:

- range of operating frequencies from 2 MHz to 160 MHz;
- transmitter and digital receiver based on DDS with digital quadrature detectors;
- the bandwidth of the receiver is determined by digital filters and is adjustable in the range 0.1 – 2 MHz;
- the duration of the RF pulse can vary from 0.05 μs to 83 ms in steps of 10 ns;
- the time between RF pulses can vary from 0.4 μs to 298 hours in 0.1 μs increments;
- it is possible to generate RF pulses with an arbitrary shape as well as pulses for the formation of magnetic field gradients;
- the spectrometer can be connected to any computer, including a laptop, via the Ethernet interface;
- dimensions of the spectrometer 190 x 190 x 60 mm;

The spectrometer is equipped with a built-in vector network analyser for adjusting and matching the NMR / NQR sensor.

"Kazan-Nova II" works with the "Aurora" software - a powerful tool for monitoring and processing experimental data with the ability to run user scripts to automate the experiment [12].

V. EXPERIMENT

Paracetamol (PCM; name IUPAC: N- (4-hydroxyphenyl) ethanamide, C8H9NO2 or acetaminophen) is a widely used analgesic and antipyretic. It produces more than 80 trademarks (Panadol, Tylenol, Lekadol, Plicet, Daleron, Lupocet, etc.) in the form of tablets, capsules, powders and liquid suspensions. Huge popularity led to the fact that paracetamol is actively forged. There are a lot of cases of treatment of counterfeit paracetamol in recent years [5, 13]. In Tab.1. frequency of paracetamol at room temperature

TABLE I
NQR FREQUENCIES OF TRANSITIONS, LINE WIDTH AND PARACETAMOL RELAXATION TIME

NQR frequencies, ν, (MHz)	Δν, linewidth (kHz)	T1, (s)
2.564	1.4	11
1.921	1.8	5
0.643		

The sensor was a solenoid coil with a diameter of 13 mm and a length of 55 mm. Paracetamol of various manufacturers was investigated. Figure 4 shows the NQR spectra of the free induction decay signal (FID) of paracetamol produced in Italy (brand Paralen) and Russian-made (Novosibirsk) from the active substance containing 500 mg.

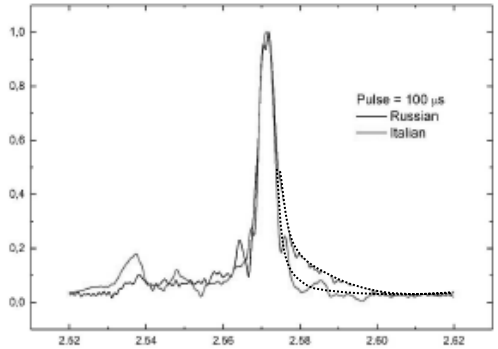


Fig.4. FID signals (in pu) of Italian and Russian paracetamol samples. The used pulse length was 100 usec.

VI. CONCLUSIONS

According to the spectra obtained, our experimental setup allows not only to uniquely identify drug compounds, but also allows to distinguish drugs produced by various pharmaceutical companies. This allows to create a refined and expanded database of reference spectra using the "Kazan-Nova II" spectrometer and design a new portable and compact drug scanner. This new class of devices will expand the instrument base of control and analytical laboratories (especially mobile) of various departments for non-destructive quality control and the authenticity of medicines.

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