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terahertz technique, THz-TDS, SCADA, polymorphism, PID cascade, Piroxicam

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ADVANCED SCADA SYSTEM APPLIED TO TERAHERTZ TIME DOMAIN SPECTROMETER

Modern pharmaceutical industry must face the problem of drug molecules decomposition and polymorphic phase transitions, changing the physical and chemical properties of the active pharmaceutical ingredient (API). A hydration-caused reduced shell life due to a humidity in a production line leads to a product waste, thus making the medicines more expensive. In order to overcome these problems, the terahertz spectroscopy can be utilized. The described control and acquisition system controls automatically the temperature of the pharmaceutical samples.

As it is known, the THz technique not only fulfills the gap between optics and radio-techniques, but it also creates a link between chemistry and physics, respectively [1]. Pharmaceutical and pharmacological sciences are gratifying domains of terahertz investigations. There can be found many significant phenomena possible to examine with a THz technique [2]. In this paper, we consider one field of the THz technique - a time domain spectroscopy (THz-TDS) [3], which is complementary to a Raman spectroscopy.

Presented samples heating system with a SCADA application constructed by the author cooperates with a custom Terahertz Time Domain Spectrometer providing a fully automated pharmaceutical samples investigation system. Piroxicam derivatives have been measured in the THz-TDS technique with an increasing temperature controlled by the designed SCADA system. A migration of the absorption peaks has been observed, indicating a molecule decomposition.

1. INTRODUCTION

1.1. CONCEPT, TERAHERTZ WAVES

Easy repeatability of the experiment, fast data logging and complicated signal processing creates a demand for non-industrial SCADA systems, applied for

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the physical, chemical and medical fields of sciences. Especially the terahertz investigations can utilize such systems eliminating a time-consuming human supervision.

A terahertz pulse propagating in the dry air and passing through a pharmaceutical pill, changes its shape because of the unique optical properties of the medicine being investigated. A tool to connect the time domain and frequency domain - Fourier transform – allows to exchange the pulse shape into the power spectral density.

1.2. SCADA, SCHEMATIC, OPERATION

Following the definition established by The National Communications System in [4], an acronym SCADA stands for *Supervisory Control and Data Acquisition*. Contemporarily SCADA systems are used widely to monitor and control plant or equipment in the industry.

Complex organic compounds can have many derivatives. Thermodynamic tests of such compounds are time-consuming because of two reasons: quantity and time per one derivative sample. Phase transitions are energy-activated and a very precise temperature control without overheating and an adequate time-temperature logging must be performed. Application of the SCADA system can make such testing fully automated and repeatable, improving a quality of the experiment. On the basis of the above considerations, a general concept of the SCADA system applied to a heating process of the pharmaceutical samples was born and is presented in figure 1.

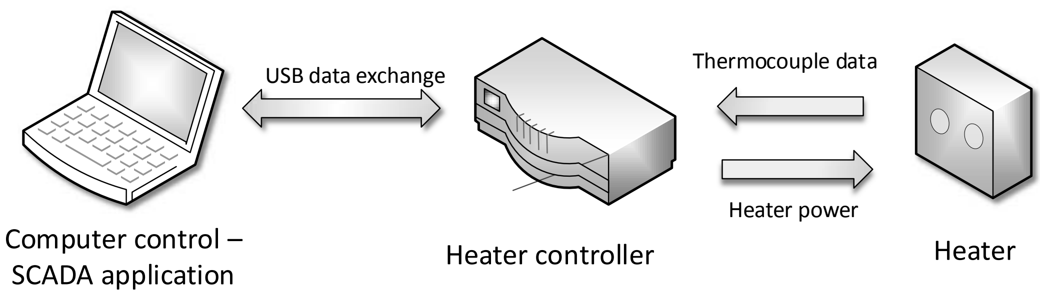

Fig. 1.General SCADA system concept

1.2. HARDWARE PART OF SCADA SYSTEM

Figure 2 shows a block diagram of the designed device. Its heart is the ARM Cortex-M4 STM32F303RCT6 microcontroller, responsible for a multi-interface communication with the peripheral devices such as memories, thermocouple sensors, platinum resistance thermometers, data exchange with a master PC application via a USB interface and a temperature control of the heaters and pills.

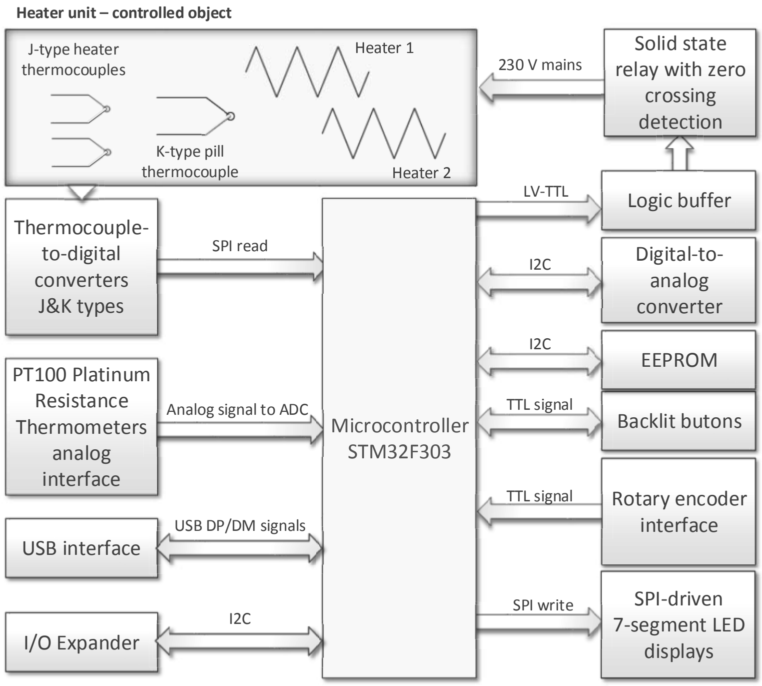

Fig. 2. Block diagram of the controller

1.2. SOFTWARE PART OF SCADA SYSTEM - APPLICATION

In order to meet the requirements of the SCADA system, a supervisory application with a graphical user interface has been implemented in a Labview environment. Its purpose was to send to the device a desired pill temperature, observe the temperature response of the pill and heaters, define a temperature profile for the experiment and cooperate with a spectrometer. It is capable to log a control process including the temperatures of the sensors and trigger a measurement of the spectrometer.

2. PILL TEMPERATURE CONTROL ALGORITHM

A simple single-stage PID controller works fine with the fast-response objects. Thermal processes with a large thermal mass provide a significant time delay in a response. An integral block in such systems saturates and leads to an effect called *the integral windup*. In the near-setpoint process values the oscillations remain and an accurate control of the heater is not possible. In a cascade structure shown in figure 3, output of one controller sets the value for the following one. Thermal response from the heater is fast in comparison to the pill. An inner control loop stabilizes rapid changes of the heater's temperature value, whereas the outer loop integrates the error of the pill temperature and provides a set point for the heater temperature. In the designed controller, both heater and pill temperatures are available, thus the PID cascade control can be applied.

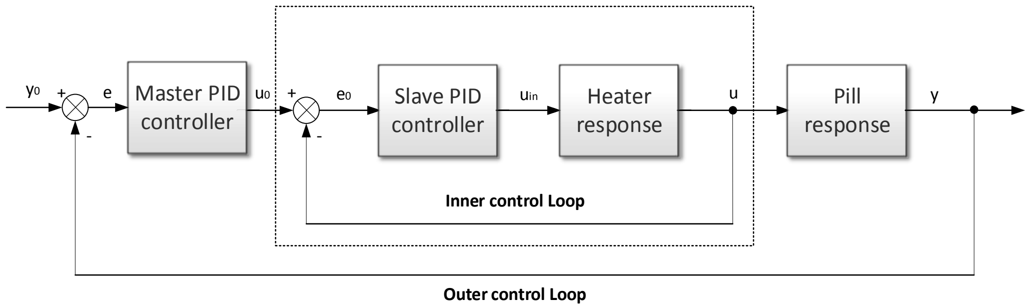

Fig. 3. PID cascade control schematic

Such approach reduces a time constant of control and results in lower oscillations [5]. In the constructed device, such control structure is found to provide the lowest temperature oscillations around the set point in the steady state as shown in figure 4.

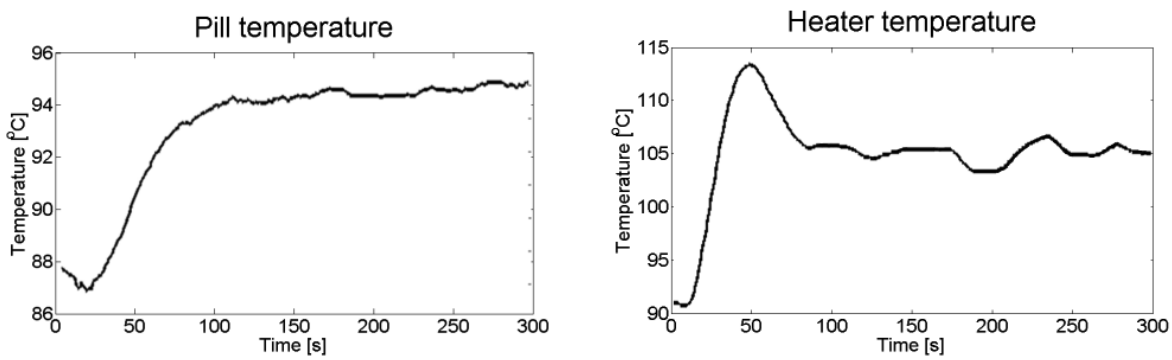

Fig. 4. PID cascade set point change responses

3. THZ-TDS MEASUREMENTS, APPLICATIONS

The designed system has been applied to determine the optical parameters of piroxicam derivatives and their spectra versus temperature. Heated samples have been scanned in the terahertz time-domain spectrometer and post-processed in a Matlab environment.

3.1. PIROXICAM, DERIVATIVES, GOAL, APPLICATIONS

Piroxicam is a nonsteroidal anti-inflammatory drug used to treat arthritis and other inflammatory conditions [6]. Crystalline piroxicam is polymorphic and exists in various crystalline forms designated as form I, form II, form III, and monohydrate form. Form III is thermally unstable and can be converted to form II and form I, respectively. Additionally, the monohydrate form can dehydrate to form I [7]. Generally, the polymorphic form of a drug can transform to a more stable form during storage and manufacturing process, such as drying, milling and compaction. Moreover, these crystal structures can have different chemical and physical properties.

Searching for more effective and safer analgesic drugs six new piroxicam derivatives were synthesized [8].

Piroxicam derivative marked as 5p + tail 3 mixed with a polyethylene powder formed a pill of weight 400 milligrams and mass concentration equal 10%. Its structural formula is presented in figure 5.

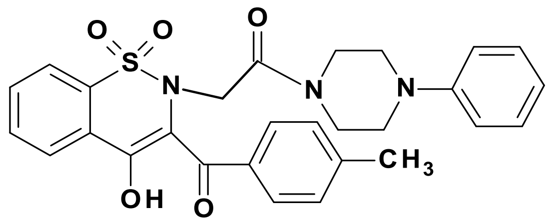

Fig. 5. Structural formula of the investigated piroxicam derivative (5p + tail 3)

Results of the THz-TDS temperature measurements are presented in figure 6. There are two wide absorption peaks evolving with temperature. The peak at 22 cm^{-1} is migrating to higher wavenumber regions by about 0.5 cm^{-1}. The wide absorption peak at 46 cm^{-1} disappears at higher temperatures, indicating an invertible molecule decomposition. It should be mentioned, that heavy molecules, to which piroxicam belongs, exhibit wide absorption lines, thus can distinguished from the narrow water lines present in the 57 cm^{-1} region. A molecule decomposition detected by the THz-TDS technique is not detected by the differential scanning calorimetry (DSC), proving a superiority of the proposed investigation technique.

4. CONCLUSIONS

Terahertz techniques can support modern pharmaceutical industry in the detection of an uncontrolled molecule decomposition. It can be observed that spectra of the molecules evolve with temperature, proving the necessity of the heat-related experiments.

Temperature control of the large thermal mass objects is a challenging task. Non-linearity in a heating process makes the control very sophisticated. Concepts far from a simple PID algorithm should be utilized. Implemented heating control process system, constructed by the author allows for thermodynamic pills investigations.

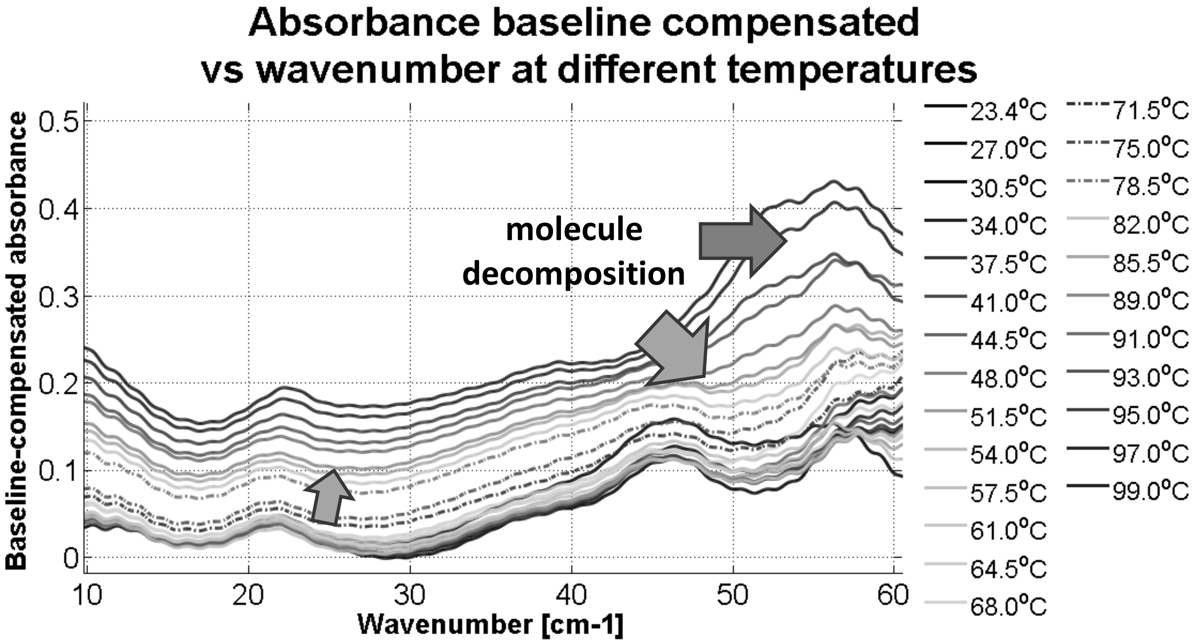

Fig. 6. Baseline-compensated absorbance of the Piroxicam derivative

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