STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

ANALYSIS OF RIMANTADINE HYDROCHLORIDE BY NEAR-IR SPECTROSCOPY

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The possibility of using near-IR spectroscopy and discriminant analysis for the identification of rimantadine hydrochloride substance and determination of the substance and tablet manufacturers has been studied.

Key words: drug, rimantadine hydrochloride, substances, tablets, near-IR spectroscopy, discriminant analysis.

Near-IR (NIR) spectroscopy has a long history but has been widely used to analyze drugs only in the last decade [1]. The stimulus for this has been mainly the invention of appropriate instruments and their combination with quantitative methods for processing spectra of compounds.

Rimantadine hydrochloride, an adamantane derivative, was selected for the present study. Rimantadine hydrochloride is used as an anti-inflammatory agent and is effective against various strains of flu A viruses, *Herpes simplex* type 1 and 2 viruses, and Flaviviridae tick encephalitis viruses. Its polymeric structure provides prolonged circulation in the organism. This enables it to be used as a prophylactic agent.

Our goal was to study the ability to use near-IR spectroscopy to analyze substances and tablets of rimantadine hydrochloride.

EXPERIMENTAL

We studied:

Rimantadine hydrochloride substance (six batches, five manufacturers): AO Olainfarm (1), Shandong Xinhua Pharmaceutical Factory under contract to Shandong Oriental International Trading Co. Ltd., China (2), Thai Wuhan Pharmaceutical Factory, China (two batches) (3, 4), Zhejiang Kanyu Pharmaceutical Co. Ltd., China (5), and Shandong Xinhua Pharmaceutical Factory, China (6).

Rimantadine hydrochloride tablets (seven batches, four manufacturers): OAO Biosintez, Penza (one batch), OOO Rozfarm (three batches), AO Olainfarm (two batches), OAO ICN Tomskkhimfarm (one batch).

Studies were conducted on an Antaris II IR-Fourier spectrometer (Thermo Electron Corp., Intertek, USA) with an integrating sphere, resolution 8 cm^{-1}, number of scans 16, measurement range 4,000 – 10,000 cm^{-1}, baseline from a Teflon standard, number of scans 32. Results were processed by a quantitative method using the TQ Analyst program (discriminant analysis, Mahalanobis distance 3, probability 95%).

Substance analytical method. A layer of substance (4 – 6 mm) in a special closed cuvette was placed into the integrating sphere. The spectrum was recorded at least 10 times for each sample, stirring it before each measurement.

TABLE **analytical method.** A tablet was placed in the integrating sphere and attached using a special device. The spectrum was recorded. Ten tablets from each batch were analyzed, measuring each tablet at least three times.

RESULTS AND DISCUSSION

The range of combination vibrations (from 5,000 to 4,000 cm^{-1}) in the spectrum of rimantadine hydrochloride (Fig. 1) had four bands at wavenumbers 4018, 4199, 4257, and 4335 cm^{-1} that were due to combination vibrations of C–H; C–C, C–H; and C–H, N–H groups. Bands at wavenumbers 5668 and 5812 were first overtones of CH_2

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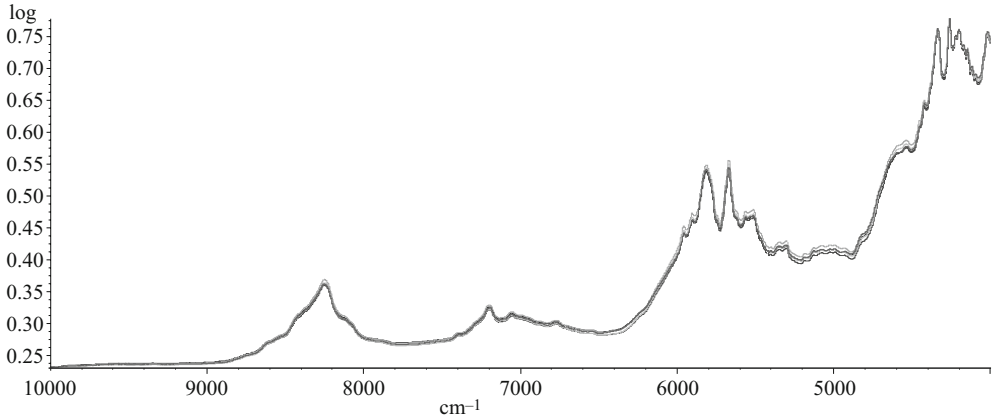

Fig. 1. Near-IR spectra of rimantadine hydrochloride substance from five manufacturers.

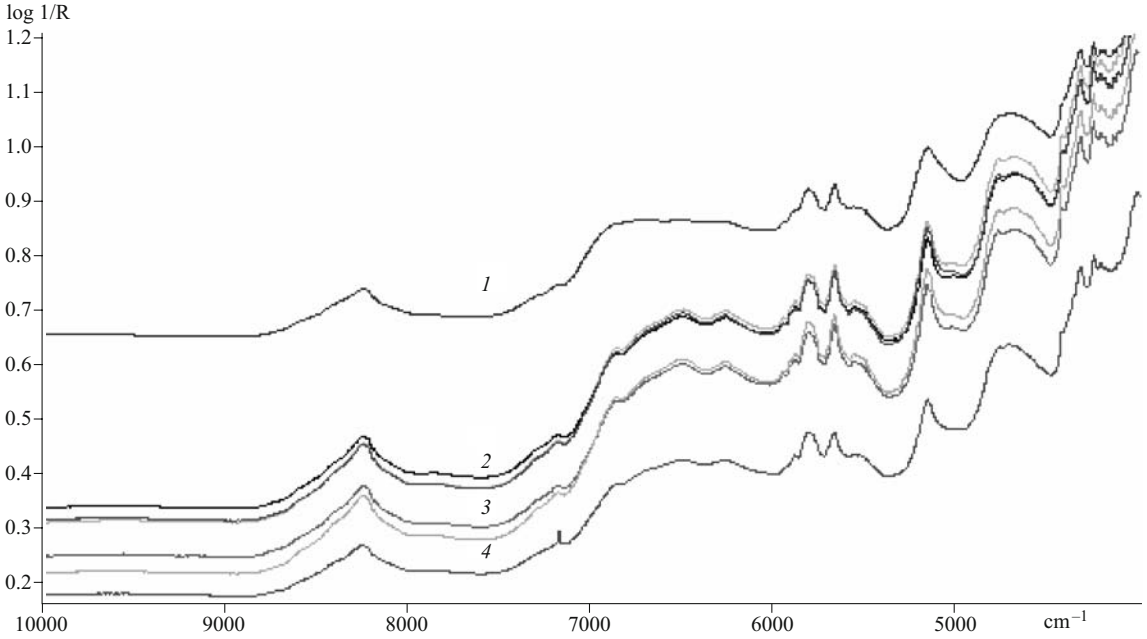

Fig. 2. Near-IR spectra of rimantadine hydrochloride tablets: OAO Biosintez, Penza (one batch) (*1*), OOO Rozfarm (three batches) (*2*), AO Olainfarm (two batches) (*3*), OAO ICN Tomskkhimfarm (one batch) (*4*).

groups. Apparently the first overtone of C–H combination vibrations appeared as a broad band at 7197; the second overtone of this group, at 8250.

Spectra of rimantadine hydrochloride tablets from all manufacturers were similar in this region (Fig. 2). Rimantadine hydrochloride in them exhibited two weak bands in the combination vibration region (4257 and 4325 – 4326 cm^{-1}), two bands in the first-overtone region (5668 – 5670 and 5815 – 5817), and a broad band in the second-overtone region (8251). A weak band at wavenumber 7185 in the near-IR spectrum of tablets from OAO ICN Tomskkhimfarm was due to the presence of talc in them.

The bands of rimantadine hydrochloride were shifted slightly in spectra of tablets compared with those of substances. This may have been due to excipients contained in them.

Obviously rimantadine hydrochloride must be extracted from the tablets and concentrated in order to confirm its authenticity.

Identification of a substance or drug manufacturer is one of the problems that can currently be solved using near-IR spectroscopy [1]. This is due to the emergence on the pharmaceutical market of many counterfeit drugs. This problem can be solved using a quantitative method to process spectra

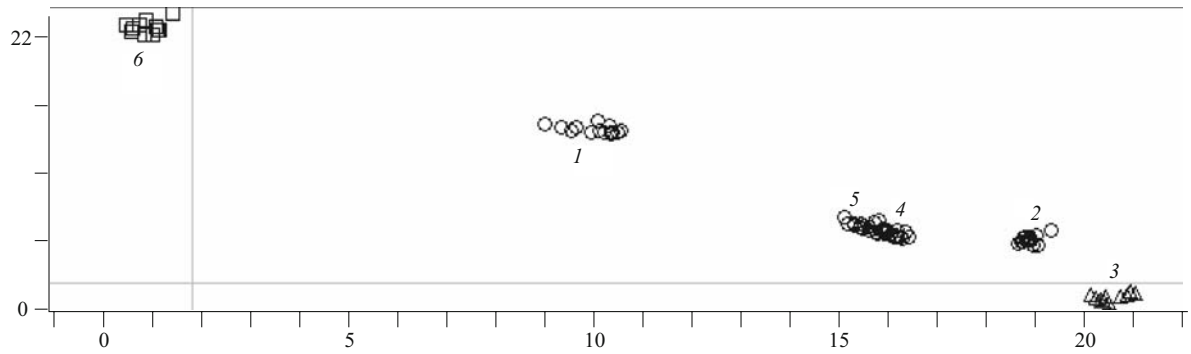

Fig. 3. Discriminant analysis of rimantadine hydrochloride substances from AO Olainfarm (*1*); Shandong Xinhua Pharmaceutical Factory, China, under contract to Shandong Oriental International Trading Co. Ltd., China (*2*); Thai Wuhan Pharmaceutical Factory, China (*3*, *4*); Zhejiang Kanyu Pharmaceutical Co. Ltd., China (*5*); and Shandong Xinhua Pharmaceutical Factory, China (*6*).

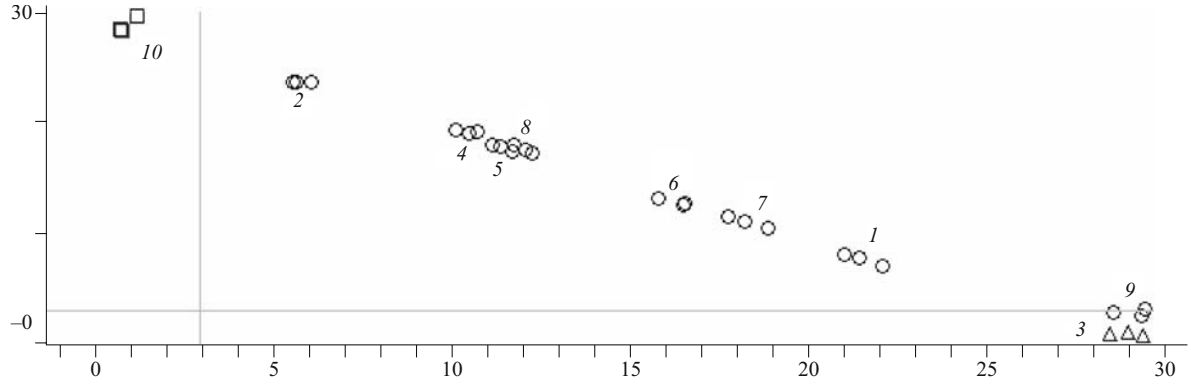

Fig. 4. Discriminant analysis of rimantadine hydrochloride tablets from a single batch.

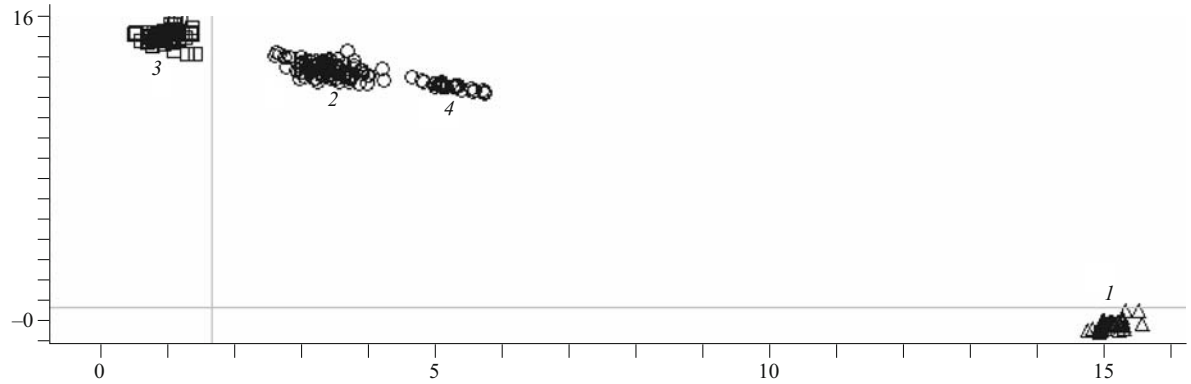

Fig. 5. Separation of rimantadine hydrochloride tablets by manufacturers using discriminant analysis: OAO Biosintez, Penza (*1*), AO Olainfarm (*2*), OOO Rozfarm (*3*), OAO ICN Tomskkhimfarm (one batch) (*4*). Discriminant analysis.

of drug samples. In the present study, discriminant analysis, which is a quantitative method, was used.

In the first step, spectra of each sample of rimantadine hydrochloride substance were checked for homogeneity. Substance samples 3 and 6 each had one result that was outside the limits of the discriminant group (Mahalanobis distance 3). These results can be explained as a mesaurement artifact or an uneven dispersion of the studied powder.

Analysis of spectra of rimantadine hydrochloride substance from different manufacturers (Fig. 3) showed that samples 4 and 5 were united into one discriminant group (Mahalanobis distance < 3). This indicated that their manu-

facturing processes were similar. The other samples were divided distinctly into groups. Of these, two batches produced by a single manufacturer (samples 3 and 4) fell in different discriminant groups. An analogous situation arose for the manufacturer of samples 2 and 6. Sample 2 was produced under contract to another company.

TABLEts were compared within batches and between batches and manufacturers.

Only one batch of tablets formed a single discriminant group (Mahalanobis distance). In one batch the Mahalanobis distance between tablets even reached 30 (Fig. 4). The distance between separate tablets in the other batches was between 6 and 8. These tablets could be divided into 2 or 3 discriminant groups. The reason for such discrepancy between tablets of a single batch was probably due to a heterogeneous tablet mass or poor tableting.

TABLEts of rimantadine hydrochloride from three batches from OOO Rozfarm were combined into one discriminant group. Two batches from AO Olainfarm were divided into two groups.

However, tablets were divided by manufacturers regardless of the discrepancy within and between batches (Fig. 5). The drug from OAO ICN Tomskkhimfarm (Mahalanobis distance 10) was clearly separated the most. The Mahalanobis distance between the other drugs was 4 – 5, which also indicated that they were reliably divided.

Thus, the studies showed that near-IR spectroscopy can be used to confirm the authenticity of rimantadine hydrochloride substances. The combination of near-IR spectroscopy and a quantitative method can identify the manufacturer of rimantadine hydrochloride substance or tablets. It was shown that the technology for preparing rimantadine hydrochloride tablets needs to be optimized.

ACKNOWLEDGMENTS

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