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Peak window correlation method for drug screening using Raman spectroscopy

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ABSTRACT

Modern portable and hand-held Raman spectrometers that recently have become widespread in drug quality screening have good reproducibility and are able to detect small concentrations of substances in mixtures of several components or distinguish compounds similar in structure and having minimal differences in spectrum with appropriate mathematical processing methods. Among other spectrum comparison approaches, the peak search at their location is the most important task of spectral imaging of the studied samples. In this work, the Raman spectra of liquid drugs involved in the governmental non-destructive quality screening program performed by 8 mobile laboratories equipped with Raman spectrometers with uncooled detector and a 532 nm laser were compared with reference sample spectra using the peak windows correlation (PWC) algorithm developed in this work by authors. The proposed method provides accurate identification, detection of composition changes, and presence of foreign components in drugs formulations even if their contribution to the overall signal is negligible. The spectral correlation method called hit-quality index (HQI) method conventionally used for such portable spectrometers was specified as comparative method.

1. Introduction

Modern period of medicine offers increasing number of new drugs every year. Meanwhile the number of counterfeit, falsified and substandard pharmaceuticals is growing. The Global Surveillance and Monitoring System for substandard and falsified medicines, vaccines and in vitro diagnostic tests (GSMS) has received up to date the reports of more than 1500 substandard products [1]. Thus, a strict control of the whole pharmaceutical supply cycle is required [2]. This can be solved by various rapid test methods based on portable devices that allow quality assurance in close proximity to consumers, e.g., in pharmacies, medical facilities, pharmaceutical warehouses, etc. They will enhance public safety by significant increase of the number of products subjected to the analysis usually taken less than three minutes. In particular, Raman spectroscopy has proved to be a powerful and convenient tool in such applications. Portable Raman spectrometers conveniently used for sample identification and counterfeit detection can perform non-destructive screening through packaging and keep samples intact for their further return to the customer [3].

Drug sample identification most frequently utilizes correlation based methods in the spectroscopy. They are successfully applied for quality control of drugs where sample spectrum is compared with that of the reference from the spectral library [4]. Correlation offers high robustness commonly sufficient for monitoring particular drugs and commonly requires rather inexpensive devices outside the laboratory. However, such approaches do not always allow differentiating compounds with similar chemical structure or determining low quantities of additional components in the sample. These problem can be solved and method sensitivity enhanced by some data treatment algorithms, e.g., moving window correlation [3,5], peak search, various types of multivariate calibration, etc.

Peak detection and parametrization are most important stages in the signal pre-processing and identification in many methods of instrumental analysis [6–8] used in analytical chemistry, physics, medicine and many other fields [9,10]. Gaussian function combined with other functional dependences is often applied for the peak parametrization [11]. Gaussian distribution allows modelling the peak shape, and its modifications are used for the most accurate

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description of complex peaks, including finding overlapped peaks in the spectrum.

The key problems in peak search are associated with their separation from the noise. In this case, the Gaussian function or its combinations are applicable in the integral convolution of the signal. Derivative methods are most popular for automate peak searching. Besides, these functions serve as noise filters. Savitzky-Golay method, Fourier transforms, wavelet transforms with the "Mexican hat" function (MHWS) [12] can be mentioned in this respect.

The moving window correlation methods are promising identification of various organic substances including drug substances. The moving window correlation shows better sensitivity and selectivity against simple correlation [5]. However, its use is limited by complexity of the optimal moving window parameter that is adjusted for each specific compound, by need of extensive mathematical calculations and difficulty of transferring models to some devices. This complicates the application of this approach in the field.

In this work, we have developed and [presented a new method of the peak window correlation (PWC) for the drug identification. This approach is a combination of two algorithms (search for extraneous peaks Rspc, and verification of the presence in the analysed spectrum of the peaks from reference sample spectrum, Rmdl). Such an approach combines all the advantages of correlation methods and includes the algorithm for the peak search in the sample spectrum. PWC being by definition an easily interpreted analog of the window correlation method solves the problem of the optimal parameter determination. The window is selected automatically at the step of peaks search in the spectrum.

Main objective of the present work was to develop spectrum analysis algorithm able to detect small concentrations of foreign substances in the drug and distinguish compounds similar in their structure and having minimal difference in spectrum that are beyond the scope of standard correlation methods. It is expected that the method proposed is not sensitive to changes in microenvironment, laser stability and other experimental conditions.

2. Methods and experiments

2.1. Materials and equipment

Both chemical reagents and original drug samples were used in the work. Samples of drugs and excipients were purchased or obtained from manufacturers, as well as selected from distribution points under the state control. Samples of original drugs was used without further preparation except for the batch solutions containing contaminated reference drugs which were prepared in laboratory as described below. The list of the samples is given in Table 1.

Raman spectra were recorded, processed and analysed using the hardware-software complex M̈ini-Ram 532, which included portable Raman spectrometer EnSpectr R532++ with spectral range of 200–4000 cm^{-1}, resolution of up to 20 cm^{-1}, 532 nm laser as radiation source and software UniQue-Lab™ developed by the Reference Center for Testing, Recording and Circulation Control of Medical Drugs and Devices (Federal Service on Surveillance in Healthcare and Social Development of Russian Federation). The spectra used were recorded on 14 instruments including those installed in mobile laboratories (Fig. 1). The spectrometers used have an uncooled matrix, and the spectra obtained in the field have a certain shift in the wave number and a different signal-to-noise ratio.

For a comparative evaluation of the PWC algorithm developed, the correlation calculation algorithm (HQI) was used.

Method was tested using spectra library of original Russian and foreign drugs including 500 references collected by the Reference Centre for Testing, Recording and Circulation Control of Medical Drugs and Devices.

2.2. Experiment description

To study the algorithms for detection of impurities in the samples tested, batch solutions were prepared. As a Model-Additive pair, samples were selected so that the addition of an additive to the

Table 1
List of used reagents.

Reagent	International non-proprietary name	Concentration	Units	Manufacturer	Manufacturer number
Ethanol	Ethanol	95	% v/v	Bryntsalov CJSC	
Propanediol-1,2		100	%	Merck	822324
Propanol-2		100	%	Sharlab	AL0321
Ammonium thiocyanate		5	%	Acros organics	A0339552
Magnesium sulfate heptahydrate	Magnesium sulfate heptahydrate	250	mg/ml	Microgen FGUP	T1140515
Dimethylsulfoxide		100	%	Sharlab	15394808
Metronidazole	Metronidazole	5	mg/ml	Synthesis JSC	846016
Meldonium	Meldonium	100	mg/ml	Moscow Endocrine Plant FSUE	370714
Drotaverine	Drotaverine	20	mg/ml	Borisov Medical Preparations Plant OJSC	
Deionized water		100	%	Millipore	
Piracetam	Piracetam	200	mg/ml	Belmed preparations RUP	
Cyclohexane		99.8	%	Ekohim	
Sulfocamphocaine	Procaine + Sulfocamphoric acid	50.4 + 49.6	mg/ml	Pharmstandard-UfaVITA OJSC	
Novocaine	Procaine	20	mg/ml	Biochemist JSC	
Novocaine	Procaine	2.5	mg/ml	Biochemist JSC	
Lidocaine	Lidocaine	20	mg/ml	Ellara Ltd.	
Lidocaine	Lidocaine	100	mg/ml	Ellara Ltd.	
Glucose	Glucose	50	mg/ml	Research and Production Complex ESKOM JSC	
Glucose	Glucose	400	mg/ml	Research and Production Complex ESKOM JSC	
Cardioxipin	Methylethylpiridinol	30	mg/ml	Biosynthesis OJSC	
Mexidol	Ethylmethylhydroxypyridine succinate	50	mg/ml	Armavirskaya biofactory FGUP	
Ethoxydol	Ethylmethylhydroxypyridine malate	50	mg/ml	Synthesis OJSC	