“十三五”国家重点出版物

Development and Application of Rapid Drug Detection Technology

药品快速检测技术研究与应用（英文版）

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·北京·

The Rapid Drug Detection Technology (RDDT) described in this book includes noninvasive near-infrared (NIR) spectrometry method and rapid HPLC analysis.

Part Ⅰ includes 4 chapters: NIR spectrometer, NIR analytical methods, application of NIRs in pharmaceutical analysis and the prospect of NIRs. Part Ⅱ focuses on the principle and application of rapid HPLC forensic method.Rapid forensic method can rapidly detect SF medicine, including rapid high-performance liquid chromatography (HPLC) and rapid liquid chromatography-mass spectrometry (LC-MS) methods.

This book is useful for scientists working in the field of drug analysis, and could be served as reference tool for drug regulatory authorities. It also could be used as training material for drug quality control practitioners and text book for students majoring in pharmaceutical science.

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Preface

The spread of substandard and falsified (SF) medicines, as defined by the World Health Organization (WHO), has been and continues to be a growing global concern. SF is a global public health threat that has grown fast in recent years due to more sophisticated counterfeiting methods and remarkable similarity of falsified products to the genuine ones, which deceive health professionals as well as patients. Their prevalence in the public, private and informal market sectors threatens global public health by jeopardizing patient safety, diminishing confidence in health systems, increasing treatment failure, wasting valuable resources and contributing to the development of drug resistance. Eliminating SF is a considerable public health challenge. In order to detect poor quality medicines, developing countries urgently need quick, easy-to-use and effective screening methods to detect poor quality medicines throughout the supply chain and in the field of rural areas.

In order to combat the SF and to protect the health of people living in rural areas, following the instruction of the National Medical Products Administration (NMPA) China, the National Institutes for Food and Drug Control (NIFDC) collaborating with several provincial and district drug testing institutes have been studying and developing a number of rapid drug testing technologies which could be used at manufacturing plants, in the field, in warehouses, at border crossings, and in pharmacies to empower regulators, manufacturers, distributors, pharmacies, procurement agencies and other stakeholders to screen for medicines.

The Rapid Drug Detection Technology (RDDT) described in this book includes

noninvasive near-infrared (NIR) spectroscopy method and rapid HPLC analysis. The main screening method is based on a NIR spectrometer and a pre-developed standard library of NIR spectra of selected commonly used pharmaceutical products in China. The confirmation method is based on patented green HPLC system and a pre-developed database. RDDT has been widely used in China, almost covered the whole geographical territory. Due to the simple, fast and easy-to-grasp features on operation, RDDT is capable of rapid screening chemical medicines and discriminating illegal chemicals in Chinese patent drugs. In this case, making RDDT more accessible will have a great help on controlling the proliferation of counterfeit and substandard medicine.

This book is a summary of the experiences and achievements of RDDT acquired from our hands-on practices which could be used as teaching material for technical staffs working in basic level drug supervision and also could be served as reference book for drug regulatory authorities.

I sincerely wish the publication of the English version of this book would be promoting the further development and application of RDDT and making these technologies more accessible will help control the proliferation of SF medicines to protect global public health.

Contents

Rapid Analysis of Chemical Drugs Using the Near-infrared Spectroscopic Technology

Rapid Analysis of Chemical Drugs Using the Near-infrared Spectroscopic Technology

Near-infrared (NIR) spectroscopy is based on the absorption of electromagnetic radiation in the wavelengths range of 780-2500nm, which is between the ultraviolet-visible spectral region and the infrared spectral region (as shown in Fig 0-1).

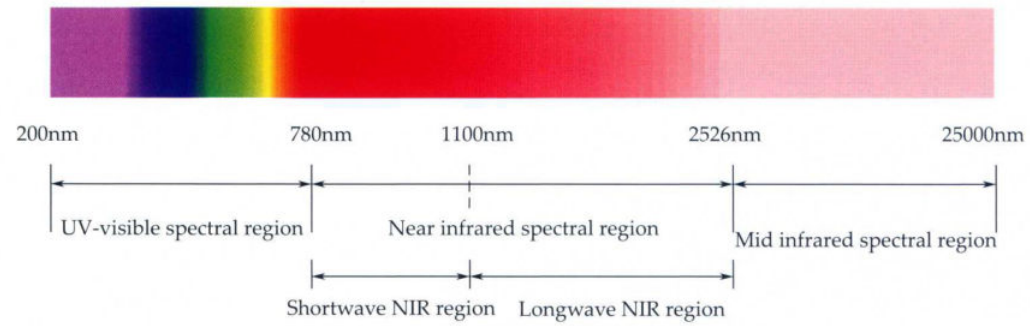

Fig 0-1 NIR region in the electromagnetic spectrum

From the aspect of the spectral energy, NIR spectra mainly correspond to the overtone and combination absorptions of molecular vibration. Quantum theory tells us that the NIR band information (frequency and intensity) depends on the anharmonicity of a molecule's structure. Due to the low transition probability of overtone and combination absorptions, the absorption signal is weak, thus only chemical bonds with high anharmonicity can be displayed in the spectra. Such chemical bonds contain the lightest atom, i.e., hydrogen atom. Therefore, the absorptions of hydrogen-containing groups X—H (X = C, N, O) dominate the NIR spectra.

In order to apply NIR spectroscopy (NIRS) in qualitative and quantitative analysis, people hope that NIR spectra could be analyzed using spectral characteristics as in other types of spectroscopies. However, through numerous tests, scientists found that the fingerprint characteristics of NIR spectra were very vague and seriously overlapped. A simple comparison between a NIR spectrum and a mid-infrared (MIR) spectrum is shown in Fig 0-2 and Fig 0-3. Obviously, the absorption peaks in the NIR spectrum show poor sharpness and are severely superimposed. There are no strong characteristic absorption peaks, so it is very difficult to conduct structure elucidation. However, in the MIR spectrum, the structure of the compounds can be basically identified through several characteristic absorption peaks, as shown in Tab 0-1.

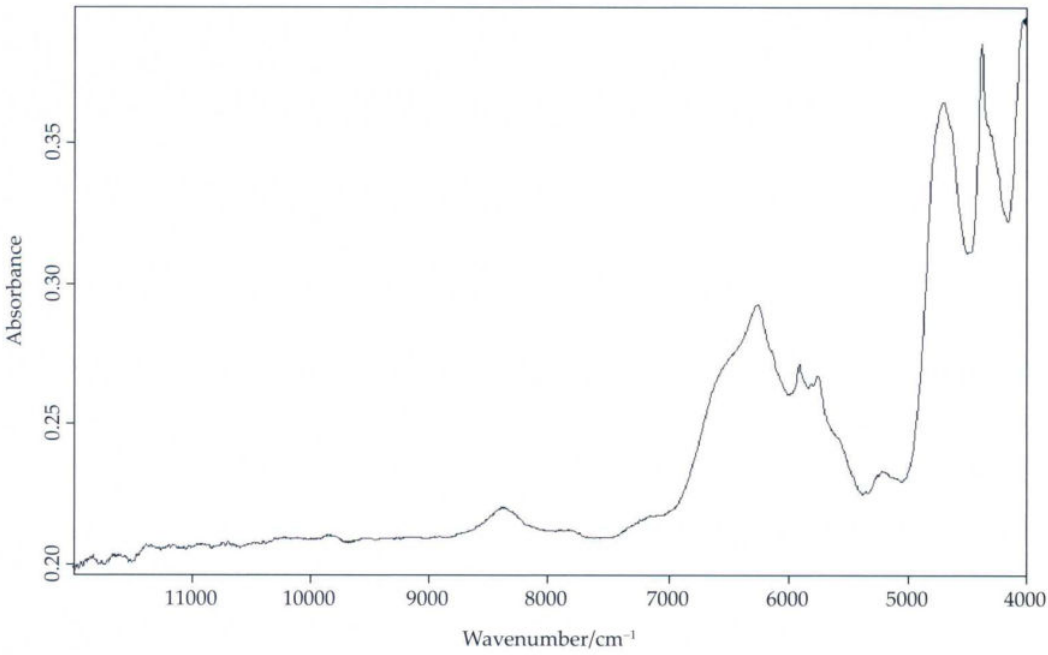

Fig 0-2 NIR spectrum of potassium sodium dehydroandrographolide succinate injection

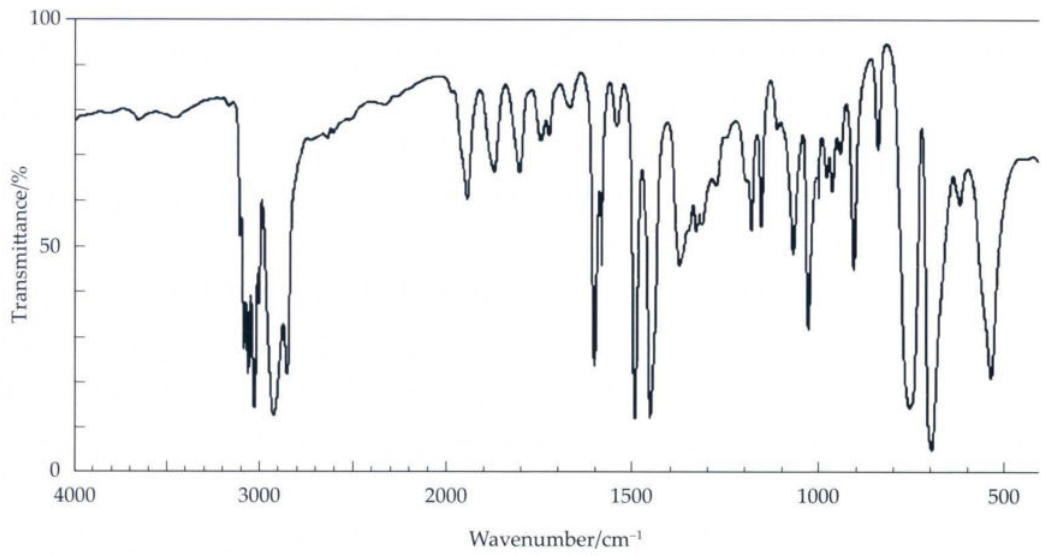

Fig 0-3 IR spectrum of polystyrene

Tab 0-1 Analysis of functional groups of polystyrene

Absorption peaks	3103, 3083···	2634	1601, 1493, 1453···	1181, 1155···
Analysis	Ar—H	CH_2	Ar—H	C—C

The above examples showed that although the NIR spectrum contains a large amount of information of the samples, traditional spectrum interpretation and

comparison methods cannot be used to identify compounds or to quantify the component concentration the way UV spectra are used. In the 1960s, Karl Norris used diffuse reflectance technique to study the wheat moisture, protein and fat, and found the practical value of NIRS methods in routine analysis. In the 1970s and 1980s the combination of chemometrics with NIR technique promoted the development of NIRS methods, which were used mainly in the field of agriculture at that time. After that, spectroscopic instrument production technology and computer technology had been greatly improved, and the application areas of NIRS were expanding constantly, thus the modern NIRS techniques were greatly developed.

NIRS technique is the combination of spectral measurements, computer science and chemometric methods. A calibration model is established by using chemometric techniques to combine the NIR signal of chemical composition or the physical data of the samples with properties determined by a standard or approved reference method. Subsequently, the composition or the properties of unknown samples are quickly predicted by measuring the spectra of unknown samples and analyzing the spectra with the established calibration model. Therefore, NIRS is an indirect analysis, which includes three factors: a reliable NIR spectrometer, powerful chemometric software, and an accurate and effective model.

We can make a simple comparison of several different methods of spectral analysis, as is shown in Tab 0-2.

Due to the strong penetration and good stability of NIR light, it is easy to obtain a spectrum of a sample, and does not necessarily require sample pretreatment. For some samples, it is even unnecessary to open the package. If a good model can be established, NIRS analysis can be extremely fast and convenient. According to recent literature, NIRS analysis has the following prominent features.

1) Non-destructive testing (non-destructive analysis method).
2) Rapid analysis (the using of chemometric methods and computer analysis can achieve real-time monitoring).
3) Multi-indicator measurement (the measurement of a variety of indicators, or

Tab 0-2 Comparison of several spectral analysis techniques

	Wavelength range	Spectral information	Method of analysis	Application
NIR	0.76–2.5μm	Combination and overtone bands of C—H, N—H, O—H	Chemometric methods	Qualitative and quantitative analysis of products, quality control of the intermediates in pharmaceutical formulation, identification of traditional Chinese medicines, plant taxonomy, etc.
MIR	2.5–50μm	Absorptions in molecular vibrational and rotational energy level	Comparison with the standard spectrum	Identification of the active pharmaceutical ingredients and chemical drugs, identification of functional groups of monomer components
UV-visible	200–760nm	Absorption induced by conjugated structure	Lamber-Beer law	Qualitative identification and quantitative analysis of drugs

the simultaneous analysis of several different ingredients).

4) Measurement of non-chemical parameters (viscosity, particle size, etc.).

5) Suitable for all kinds of test environment (the combination with fiber-optic technology and probes allows NIRS to be used for all kinds of online environments and sample forms).

However, the NIRS analysis technology has some limitations. Firstly, in order to cover the physical or chemical data range of the substances to be measured, a large number of samples must be used as the training set to establish the calibration model. A reference method is needed for the measurement of the sample properties for the training set, so the scope of NIRS application and accuracy of NIRS analysis are restricted by training samples and the reference method. Secondly, due to the low sensitivity, NIRS can only be used to analyze the main components of samples.

NIRS analysis is extensively applied in the international and domestic pharmaceutical industry, and is used not only for the analysis of chemical drugs, antibiotics, raw materials and pharmaceutical formulation, but also for the identification of Chinese herbal medicines and the decoction pieces. It is also helpful in identifying the authenticity of samples, distinguishing the quality of Chinese herbal medicines and decoction pieces, performing quantitative

analysis of Chinese traditional patent formulation, etc. It can be applied to the solid samples, as well as the liquid formulations. In addition, some of pharmaceutical companies in China are using NIRS to control the quality of intermediates and finished products.

More standardized researches should be conducted for a better application of NIRS. A standardized laboratory has been founded by the National Institutes for Food and Drug Control in China. *Chinese Pharmacopoeia* (ChP) has put forward guidelines for NIRS. From the long-term point of view, with the application and the development at the metrical level, the NIR method will have a revolutionary influence on the pharmaceutical industry.

Chapter 1

NIR Spectrometer

The prerequisite of NIRS is gaining stable NIR spectra, which is conducted on a NIR spectrometer. To obtain good NIR spectra, there are strict requirements for the stability and precision of the instrument. The accuracy of the testing results of the sample is directly related to the performance of the NIR spectrometer. Therefore, we first need to understand the working principle and main performance indicators of NIR spectrometers.

Classification and Characteristics of NIR Spectrometer

In the past fifty years, numerous changes have occurred in the design, performance and measurement methods of NIR instruments. There is a great variety of modern commercial NIR instruments with a wide range of applications, such as online detection equipments, portable NIR spectrometer, specialized or general instruments. Generally, based on the spectroscopic system, NIR instruments can be divided into the filter type, the dispersive type (grating or prism), and the Fourier transform type. The latter two are used more often in commercial instruments.

Grating NIR Spectrometer

A grating NIR spectrometer has a grating (or a prism). Holographic gratings are often used in modern instruments. Monochromatic lights of different