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REGULAR PAPER

A Review of Pharmaceutical Robot based on Hyperspectral Technology

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Abstract
The quality and safety of medicinal products are related to patients' lives and health. Therefore, quality inspection takes a key role in the pharmaceutical industry. Most of the previous solutions are based on machine vision, however, their performance is limited by the RGB sensor. The pharmaceutical visual inspection robot combined with hyperspectral imaging technology is becoming a new trend in the high-end medical quality inspection process since the hyperspectral data can provide spectral information with spatial knowledge. Yet, there is no comprehensive review about hyperspectral imaging-based medicinal products inspection. This paper focuses on the pivotal pharmaceutical applications, including counterfeit drugs detection, active component analysis of tables, and quality testing of herbal medicines and other medical materials. We discuss the technology and hardware of Raman spectroscopy and hyperspectral imaging, firstly. Furthermore, we review these technologies in pharmaceutical scenarios. Finally, the development tendency and prospect of hyperspectral imaging technology-based robots in the field of pharmaceutical quality inspection is summarized.

Keywords Pharmaceutical robot · Quality inspection · Hyperspectral imaging · Raman hyperspectral

1 Introduction

Since the COVID-19 pandemic, the great power nation of pharmacy in the world, such as the United States, the United Kingdom, Germany, and China, have successively developed vaccine products against the new coronavirus. However, the quality and effectiveness of vaccines produced from various countries are unstable. For example, it is reported that the AstraZeneca vaccine produced in the United Kingdom had a certain degree of lethal probability due to a lack of competent supervision. It casts a shadow over the epidemic and severely damages people's confidence in the new vaccine. As a consequence, it hinders widespread vaccination, which is not conducive to the early control of the epidemic. [2]. In the production process of large quantities of vaccines and other pharmaceutical products, fast, accurate, and comprehensive quality and effectiveness inspection methods will become indispensable and important for the pharmaceutical industry. Therefore, the medicine and vaccine inspection techniques have gradually become active research area in this specific era [1].

The quality and effectiveness inspection of medicine mainly includes the detection of the counterfeit drug of biomedical reagents, the quality inspection of medicinal materials such as herbal medicines, the active component analysis of tables [3]. Previous pharmaceutical detection methods are mainly concentrated in the field of machine vision, in which the image data of the solid-state tablets and liquid reagent bottles can be obtained by the way of irradiating or transmission imaging with industrial cameras. The machine vision-based inspection techniques have achieved huge success and commercial benefits, however, there are numerous limitations. The main challenge refers to the imaging principle of visible light cameras. Because the standard industrial camera only takes three discrete spectral band images, i.e., red, green, and blue. Although the spatial information can be captured well, the different components cannot be easily classified. For example, the foreign anomaly or denatured drugs are often not effectively

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detected, especially when the color of target objects or denatured drugs are consistent with normal patterns [4, 5].

Hyperspectral imaging can offers consistent spectral band images according to the reflectance and absorbance of substances under different wavelengths. Recently, this technology has been rapidly developed and widely applied in various fields, including ground remote sensing imaging, agricultural and forestry pest control, food safety inspection, etc. [6, 7, 9]. However, the application in the field of pharmaceutical quality testing attracts less attention from researchers and developers. Although there are some methods and techniques combining the hyperspectral imaging technology in pharmaceutical quality and effectiveness inspection [10], the comprehensive review is absent. In this paper, we firstly introduce the technology and hardware of Raman spectroscopy and hyperspectral imaging-based pharmaceutical inspection robot. Furthermore, we review these technologies in pharmaceutical scenarios, such as the active component analysis of tables. Finally, the development tendency and prospect of hyperspectral imaging technology-based robots in the field of pharmaceutical quality inspection is summarized.

2 Hyperspectral Technonlogy

2.1 Technical Principle of Raman Hyperspectrum

The Raman hyperspectral analysis method was originally discovered by the Indian scientist Chandrasekhara Venkata Raman to destroy optical molecules. The analysis method uses the spectra of different incident light frequencies to analyze [10]. The Raman effect refers to the elastic and inelastic scattering of light when it irradiates a substance. Inelastic scattering has components that are longer and shorter than the excitation wavelength. Among them, the spectral lines of the inelastically scattered light that are different from the incident light frequency are called Raman lines, the Raman lines whose frequency is less than the incident light frequency are called Stokes lines, and those with greater frequency are called anti-Stokes lines.

The number of Raman spectral lines, the magnitude of the displacement, and the length of the spectral lines are directly related to the vibration or rotation energy level of the measured substance molecules, and can directly correspond to different molecular compositions. Therefore, Raman hyperspectral analysis technology is widely used in the identification of substances, such as the component analysis and authenticity identification of medicine, the structure research of biological proteins, and the identification of pesticide residues on the surface of agricultural products, etc.

During the detection, the Raman hyperspectrometer will irradiate a beam of monochromatic light on the surface of the drug to be tested, and the molecules composed of the substance will scatter the incident light. The frequency difference between the scattered light and the incident light is called the Raman shift. The Raman shift has nothing to do with the frequency of the incident light, but only with the structure of the scattered molecules themselves. Specific molecules correspond to specific Raman shifts, so Raman hyperspectroscopy has extremely high sensitivity in detecting the composition of substances [11].

2.2 Raman Hyperspectral Hardware System

Raman hyperspectrometer is also called grating dispersion Raman hyperspectrometer, which is mainly composed of excitation light source, external optical path, optical dispersion system and calculation processing system [12, 13]. Figure 1 shows the Raman hyperspectral system structure.

(1) Excitation light source:
Commonly used excitation light sources are Ar ion laser, Kr ion laser, He-Ne laser, Nd-YAG laser, diode laser, and so on. The wavelength of the Raman excitation light source is usually 325nm (UV), 488nm (blue-green), 514nm (green), 633nm (red), 785nm (red), 1064nm (IR).

(2) External optical path:
The external light path is mainly composed of optical devices such as filters and dichroic mirrors, which are used to project the Raman scattered light generated by the excitation light source irradiated on the surface of the sample to the photodetector. The

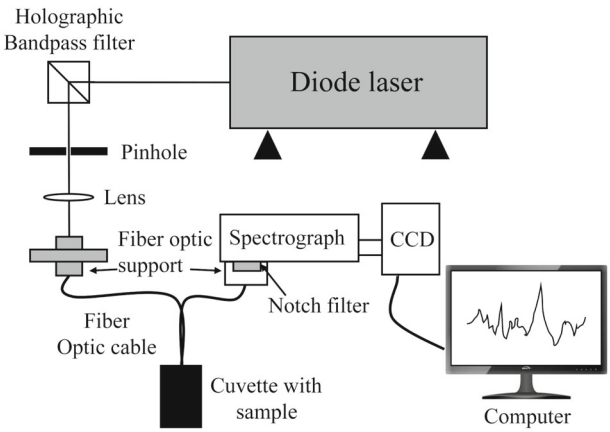

Fig. 1 Raman hyperspectral system structure figure. This system mainly consists of laser, spectrograph, CCD device and other optical devices

role of the filter is to filter out the scattered light of the excitation wavelength that is many orders of magnitude stronger than the Raman signal. In addition, it is necessary to prevent the sample from being irradiated by other radiation sources.

(3) Optical dispersion system:

The optical dispersion system is mainly composed of the entrance slit, collimator lens, dispersive optical element, exit slit, etc., and is used to decompose the polychromatic light in the light source into light with a single wavelength. The core dispersive elements are mostly grating devices, and holographic grating devices are commonly used. Most of the devices are silicon-plated CaF2 beam splitters, quartz beam splitters, or KBr beam splitters.

(4) Calculation processing system:

The calculation processing system is mainly responsible for the control of the instrument and the collection and analysis of data. At present, advanced computing and processing systems have significant advantages in sample databases and sample data analysis algorithms, and they generally integrate corresponding computing and processing software.

(5) The detector:

The detector is determined according to the wavelength range detected by the instrument. The general Raman detection of visible light uses a CCD detector and an infrared detector made of commonly used InGaAs material that involves infrared wavelength detection.

2.3 Principle of Hyperspectral Imaging Technology

Hyperspectral imaging technology and Raman hyperspectral technology have something in common. Both are based on the reaction of material molecules to light and the sensing detection of light. The difference is that Raman hyperspectrum uses The Raman displacement between scattered light and incident light to identify the molecular composition of substances, while hyperspectral imaging detects the composition of substances by imaging material surface of light in very many narrow bands [14, 15]. Hyperspectral imaging allows better visualization and enables researchers to detect some physical and chemical properties of substances more intuitively. Figure 2 shows a schematic diagram of hyperspectral imaging.

Technically, hyperspectral imaging is an image processing technology based on very many narrow-band lights. It combines imaging technology with spectral technology to detect one-dimensional spectral information of the target and two-dimensional spatial plane information, so as to obtain continuous narrow-band spectral image data with high spectral resolution.

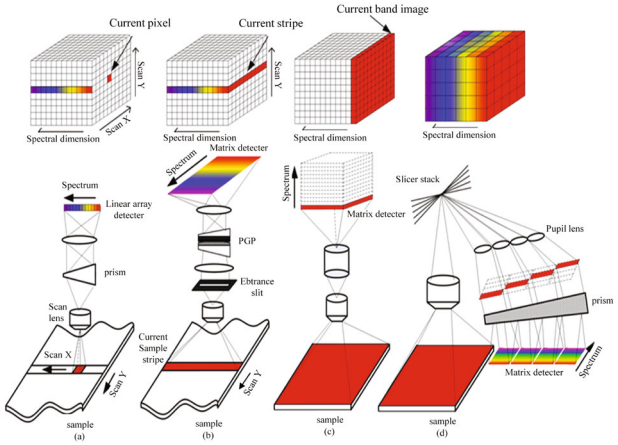

Fig. 2 Schematic diagram of hyperspectral imaging cited by [20]. In this figure, (a)indicates the whiskbroom hyperspectral imaging principle, (b)indicates the pushbroom hyperspectral imaging principle, (c)indicates the staring hyperspectral imaging principle, (d)indicates the snapshot hyperspectral imaging principle

Hyperspectral imaging technology is applied in a wide range of scenarios, including pharmaceutical detection, medical diagnosis, aerospace, food safety, and agricultural and forestry monitoring, covering all levels of social life [7, 8, 16–19]. With the improvement of the spectral resolution of hyperspectral imaging, the spectral detection ability is enhanced, and the advantages of hyperspectral imaging are becoming more and more obvious. In addition, continuous spectral reflection or transmission images make it possible for researchers to use the image pattern recognition method to extract features from objects, thus greatly expanding the application and promotion of hyperspectral technology in daily life.

2.4 Hyperspectral Imaging Hardware System

Hyperspectral imaging system is mainly composed of light source, camera and imaging control system. Figure 3 shows the hyperspectral imaging system and Table 1 shows Types and applications of hyperspectral imaging systems.

The light source can be divided into a short arc lamp, xenon lamp, Bromo-tungsten lamp, and so on. Hyperspectral camera imaging needs to detect all wavelengths of light within the imaging band range, so the luminous wavelength range of the light source must cover the wavelength range of camera imaging, and the illumination intensity of each wavelength should be relatively uniform so that the imaging system can detect and image light of each wavelength stably. Among them, the wavelength range of short-arc lamp roughly covers the range of ultraviolet to visible light, Bromo-tungsten lamp roughly covers the range of visible to near-infrared wavelengths, and xenon lamp covers a relatively comprehensive wide wavelength range of ultraviolet

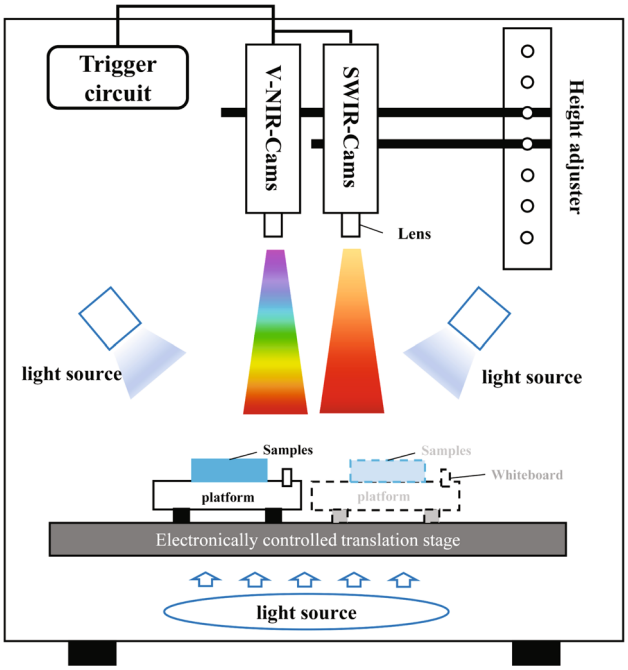

Fig. 3 Hyperspectral imaging system diagram. This diagram indicates the common layout of commercial hyperspectral imaging system which mainly consists of light source, hyperspectral cameras and other mechanical motion system

to visible and then to near-infrared wavelengths, which is an excellent all-band light source.

The camera composition of the hyperspectral imaging system is related to the types of imaging collection. There are four types of imaging collection, namely whiskbroom, Pushbroom, Staring, and Snapshot [20].

The whiskbroom hyperspectral imaging system is mostly used in the field of satellite remote sensing hyperspectral imaging. It is usually mounted on a satellite or an airborne platform and performs point-scan imaging of the ground target area through a rotating mirror. The characteristics of whiskbroom imaging make the design of the motion control system of the equipment complicated, and it is difficult to miniaturize the equipment. In addition, the single-point imaging mode is time-consuming and is not suitable for fast imaging applications [21].

Pushbroom hyperspectral imaging systems are also called line-scan hyperspectral imaging systems, which are widely used in scientific research and military scenarios such as agriculture and forestry monitoring, food and drug testing, satellite remote sensing imaging, etc. Different from the whiskbroom single-point imaging mode, the pushbroom imaging mode can obtain a line of pixel spectral data values at a time. From the device point of view, the photodetector

Table 1 Types and applications of hyperspectral imaging systems

Type	Light	Imaging	Application	Wavelength ranges	Spectral resolution	Time costs	Band numbers	Suitable for industry
Whiskbroom	sun light	point scan imaging	satellite remote military use marine research.	wide	high	long	hyperspectral	No
Pushbroom	sun light, xenon lamp, halogen lamp	line scan, imaging	drug,food, agriculture forestry remote sensing marine research pharmaceutical.	wide	high	long	hyperspectral	No
Staring	xenon lamp, halogen lamp	imaging via spectral spectral dimension	drug and food forensic image industry image seed breeding.	wide	high	long	hyperspectral	No
Snapshot	xenon lamp,halogen lamp	fast imaging	drug and food medical image, forensic image, industry image, agriculture, forestry detection archaeological AI education pharmaceutical.	wide	low	short	multispectral	yes

obtains the photoelectric signal value of a single row of pixels at a time to achieve linear array imaging when light passes through the slit. The characteristic of pushbroom imaging is that the imaging speed is significantly improved relative to the whiskbroom type. The hyperspectral image the target area can be quickly obtained in a short time, and it also maintains a high spectral dimension resolution, so this imaging system has a high market share, and much scientific research and civilian equipment platforms use this imaging method [22].

Staring hyperspectral imaging system, compared to pushbroom imaging mode, its imaging method is to obtain a single-wavelength image of the entire target area at a time and sequentially obtain the spectrum of each wavelength along with the spectral dimension spatial image, and finally, synthesize a hyperspectral data cube. The advantage of this imaging mode is that it can image at any starting wavelength and any wavelength by setting the filter. It can not only achieve full-spectrum imaging in a wide range of wavelengths, but also rapid specific wavelength imaging in a characteristic wavelength range. So it is widely used in industry and laboratories [23].

Snapshot hyperspectral imaging system is currently the most popular research point of hyperspectral imaging. The system is designed to collect all spatial and spectral information in a single exposure process, completely removing restrictions of the spatial or spectral scanning. The snapshot imaging mode removes the time limitation of scanning imaging and achieves a breakthrough in fast hyperspectral imaging. However, the imaging design of the system also limits the spectral resolution and spatial imaging range [24–26].

3 Application of Hyperspectrum in Pharmaceutical Quality Inspection

3.1 Application Scenarios of Robots in Pharmaceutical Industry

Nowadays, more and more attention has been paid to the medicine safety, and the pharmaceutical quality testing has become a key problem to be solved urgently by many pharmaceutical enterprises. However, there are many problems in the pharmaceutical process, such as complex pharmaceutical technology, high requirements for the control of bactericide, and difficult to detect the tiny pollutant particles in the pharmaceutical process [27, 28]. Therefore, it is urgent for pharmaceutical robots to independently complete the pharmaceutical and testing workflow, effectively control the degree of sterilization in the production process, improve the quality testing accuracy of pharmaceutical products, and achieve efficient independent pharmaceutical and testing operations.

At present, the application scenarios of pharmaceutical robots are mainly sterile flexible filling, sealing, vision detection, sorting and packaging and independent handling operations [29–35].

In terms of sterile flexible filling and sealing, Zeng et al., [31] proposed a positioning algorithm of filling and sealing robot based on Gaussian mixture model. Gaussian mixture model was used to cluster bottle mouth images, and the Euclidean distance between the clustering center of each image and the mean value of input data was used to give the prediction center location. This method can accurately detect the center position of the bottle mouth, which provides great convenience for the accurate filling and sealing of the pharmaceutical robot.

In pharmaceutical robot vision detection, Zhou et al., [32] proposed an automatic vision detection algorithm of glass bottle bottom with significant detection and template matching. In order to solve the problem of glass bottle bottom detection, a significance detection method was proposed to locate and search the bottle bottom defect area, and the template matching method was adopted to detect the bottle bottom circular texture area. The accuracy of defect detection by this method is 88.83%, which meets the engineering application standard and brings a new solution to the bottom quality detection of glass bottles. In addition, Zhou et al., [33] proposes a glass bottle bottom surface defect detection framework based on visual attention model and wavelet transform on the basis of [32]. The framework uses the visual attention model to detect the defect area and boundary, and uses wavelet transform multi-scale filtering algorithm to reduce the impact of bottle bottom texture. The accuracy of positioning error is improved. In terms of abnormal detection of pharmaceutical products by robots, Zhang [36] proposes a multi-model cascade method of drug particle detection depth based on CNN and random forest. For small foreign particles in liquid medicine, a multi-model cascade method of single frame combined with multi-frame images is adopted. It can improve the accuracy of foreign body detection and reduce the rate of missed detection under the background of strong noise. In addition, Chen [37] proposes a multi-scale attention-memory autoencoder network for abnormal detection. This method combines the superior performance of the autoencoder network in abnormal sample data reconstruction and the excellent feature extraction ability of the multi-scale global spatial attention module to achieve the high-precision detection effect of medical abnormal samples.

In the pharmaceutical robot sorting and packaging and independent handling operations, Patchara [38] proposed the medicine product unloading robot system, the system uses vacuum gripper and visual positioning module, to

achieve the rapid sorting and handling of medical products in a structured environment, greatly improve the production efficiency.

In general, the application of pharmaceutical robots in pharmaceutical industry has gradually become mature, and the technology application of each station in pharmaceutical production line has also made new progress. In a typical practical case [27, 28, 39], the widespread promotion of pharmaceutical robots even in the line of emergency medical products such as vaccines also confirms the development trend of the pharmaceutical industry in the future.

3.2 Raman Hyperspectral Detection Applications

Raman hyperspectral detection technology has a wide range of research applications in the field of medicine. It mainly includes active pharmaceutical ingredients detection, drug authenticity detection, drug component analysis, drug surface coating detection, etc. In addition, Raman hyperspectral detection technology mainly to solve the detection and identification problem that the traditional industrial vision can not fix. And the problem how to extract the spectral information of the drug from the Raman hyperspectral data has become the focus of the researchers [40, 41].

3.2.1 Finding the Most Valuable Detection Location

Raman hyperspectral technology can only detect a certain point on the surface of the sample during the detection process, so how to find a position with the most abundant Raman hyperspectral information for detection has become a key research issue. Zhang et al., [42, 43] introduced a dynamic sampling supervised learning method (SLADS), which iteratively finds the best sampling position and obtains the position with the richest Raman hyperspectral information, which greatly improves the imaging efficiency. This method can reduce the number of sampling pixels of the hyperspectral Raman microscope of pharmaceutical materials by 7 times, and the image quality loss can be neglected (about 0.1 % error). The combination of this method and Raman hyperspectral analysis can achieve the effect of increasing the imaging speed and strengthening the detection and analysis capabilities, which will greatly help the quality detection of drugs in the pharmaceutical process.

3.2.2 Analysis of Drug Components

In view of the analysis of drug components, researchers have proposed their analysis methods according to the different characteristics of different drug components [44–46]. Gut et al., [47] aimed at the analysis of pharmaceutical composition and combined four multivariate statistical methods PCA(principal component analysis), ICA(independent component analysis), MCR-ALS(multivariate curve resolution—alternating least squares), and NMF(Non-negative matrix factorization) to extract the spatial and spectral information of the compound from the formulation of solid pharmaceuticals. Among them, the PCA method can effectively find the source of component variation in the drug matrix. Figure 4 shows the pharmaceutical composition analysis using PCA methods [47]. And the ICA method can extract the chemical information of the drug from homogeneous and heterogeneous data sets, NMF and MCR-ALS method can better distinguish semi-quantitative information in the heterogeneous drug data set MALDI(Matrix assisted laser desorption/ionization mass spectrometry imaging). In general, these statistical methods can extract significant signals of drug composition and display the statistical distribution of tablet compounds without prior knowledge. Boiret et al., [48] proposed an iterative method to identify ingredients in medicines. This method uses spectral libraries, spectral distances, and orthogonal projections to iteratively detect ingredients in tablets. The biggest advantage of this method is that it is suitable for the analysis of low-dose components. And the method itself is based on the iterative decomposition of the signal space, it has a better detection effect under the condition of low spectral contribution and fewer pixels. This method is of great significance in detecting

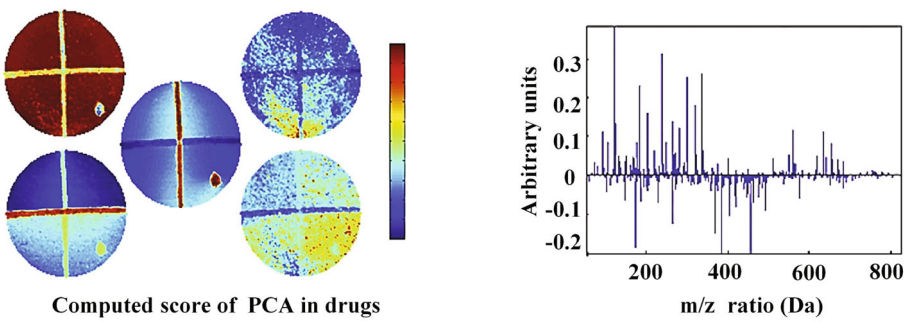

Fig. 4 Pharmaceutical composition analysis using PCA methods [47]. The left diagram indicates the computed score of PCA in drugs and the right diagram indicates the computed signals for PCA algorithm

counterfeit drugs and drug stability. Porquez et al., [49] used spectral focusing-CARS(Coherent anti-Stokes Raman scattering) hyperspectral technology to perform drug characterization experiments on ibuprofen, acetaminophen crystal form, and starch adhesives and showed the experimental results to distinguish between different drugs. This method uses broadband hyperspectroscopy and fast single-vibration frequency imaging with microsecond pixel dwell time to achieve accurate identification of the chemical crystal form of acetaminophen samples. However, the disadvantage is that this Raman microscopy detection technology takes a long time. It takes 15 minutes to obtain the imaging part of the spectrum, which affects the efficiency of analysis and is not conducive to the detection and analysis of preparations on a rapid production line.

3.2.3 Counterfeit Drugs Detection

The problem of authenticity detection of drug tablets is directly related to the life and health of patients. Counterfeit drugs not only worsen the patient's condition but can even cause death in extreme cases [50, 51]. Figure 5 shows the detection of the counterfeit drugs using the Raman Hyperspectral method [52]. Especially in relation to the detection of antimalarial drugs in poor areas, Coic et al., [53] adopt a multivariate curve resolution-alternating least squares (MCR-ALS) method to analyze the Raman hyperspectral image and Fourier transform infrared spectrogram of the drug. This method found that Raman spectroscopy is superior to Fourier transform infrared spectroscopy in elucidating compounds, analysis time, and data size, which is beneficial to the rapid authenticity detection and analysis of antimalarial tablets. Frosch et al., [54] aim at the drug safety of counterfeit antimalarial tablets, and proposed a new method of Raman hyperspectral imaging based on optical fiber array, which can directly and non-invasively quantitatively evaluate antimalarial original drugs of flumefenidine and artemether in tablets. It brings a new analytical approach to the identification and analysis of active pharmaceutical ingredients in antimalarial tablets. Coic et al., [52] proposed a pixel based method in identifing counterfeit drugs. This method identifies the essential spectral pixels in drugs' Raman hyperspectral images using convex hull calculation and it greatly decreases the amount of image data. In addition, it has a remarkable effect on the indentification of chemical component with different percentage in counterfeit drugs, and is able to realize identification taskes of counterfeit drugs reliablely in a relatively short time.

3.2.4 Detection of Active Pharmaceutical Ingredients and Coating Thickness of Tablets

The detection of active pharmaceutical ingredients in pharmaceuticals products generally refers to the quantitative determination of active ingredients in drugs. [55–57]. As for the quantitative measurement of acetylsalicylic acid in drugs, Szostak et al., [58] detected the Raman hyperspectral images of powder and tablets using the peak intensity, PCR and PLS methods which achieves excellent performance. In addition, Frosch et al., [59] proposed a novel Raman imaging detecting method which could clearly detects multiple APIs of drugs in a short time. Those APIs include acetaminophen and caffeine, and the detecting precision could reach to 1 microns which is able to obtain accurate detection results in terms of the content, shape, and agglomeration of the main active ingredients.

In addition, the concentration detection of active ingredients in liquid medicine is also essential in pharmaceutical quality. Excessive drug concentration may lead to accidents that endangers people's health, such as drug poisoning. However, low drug concentration greatly affects the efficacy of the drug, which will not only delay the optimal treatment time for patients but also cause irreversible damage to the quality of pharmaceutical companies [60, 61]. Nagy et al., [62] aim at the problem that the non-linearity in the drug Raman spectrum affects the measurement results of the concentration of drug composition, innovatively proposed a variable selection method to obtain more accurate quantitative results. This method discards the most disturbed band and retains the normal band as the spectrum range to be measured, which not only improves the accuracy of

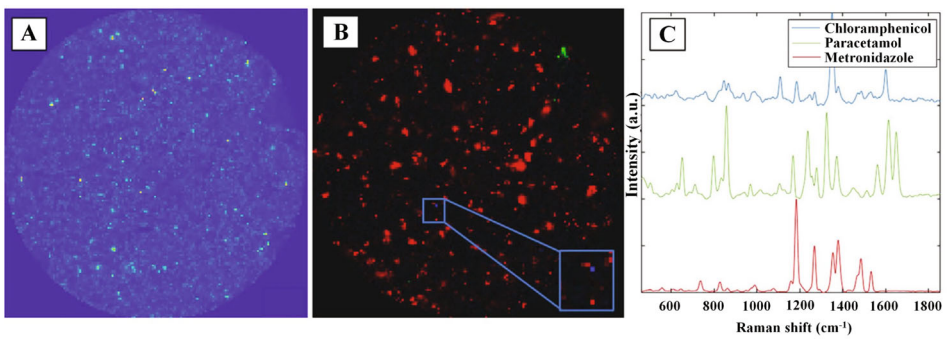

Fig. 5 Counterfeit drugs detection using Raman Hyperspectral method [52]. The figure indicates the results of the least squares projection on drugs image data. A) Initial map. B) Representation of 3 compounds elucidated by the strategy. C) Representation of the different pure spectra obtained by the strategy

concentration measurement but also enhances the linearity of the model, which provides a new idea for the treatment of drug concentration measurement.

The thickness of the drug coating plays a decisive role in the dissolution of drugs in the human body and the release of effective components. Therefore, the detection of drug surface coating thickness is an important content that cannot be ignored in drug detection by Raman hyperspectroscopy [63–65]. Figure 6 shows the detection of the coating thickness of tablets with the Raman spectroscopy method [66]. Song et al., [66] innovatively proposed a line mapping method based on space-shifted Raman spectroscopy to solve the problem of thickness detection and analysis of protective chemical coatings for drug deposition. It has achieved signal calibration and thickness prediction in terms of coating thickness of acetaminophen. This method mainly relies on the analysis of Raman intensity ratio of the light back from the coating and APIs of tablets. And it has a significant meaning for the industral fast detection of tablets' coating thickness.

3.3 Application of Hyperspectral Imaging Technology in Detection

Compared with the situation where Raman hyperspectral detection relies on spectral curves for data analysis, hyperspectral imaging technology has realized the leap from one-dimensional line spectroscopy to two-dimensional imaging plane.Not only has the amount of hyperspectral data greatly enriched but also it contains spatial plane information that cannot be obtained by Raman hyperspectroscopy. In this way, it could expand the application scenarios of hyperspectroscopy and contribute to the extended application of hyperspectral technology in pharmaceutical inspection and other agricultural and forestry, as well as forensic criminal investigation fields. Table 2 shows the applications and methods of hyperspectral imaging in pharmaceutical detection.

3.3.1 Detection of Active Pharmaceutical Ingredients

In the detection of active pharmaceutical ingredients, the detection of Raman hyperspectroscopy is limited to the sampling of surface points, and it is impossible to comprehensively and accurately detect and analyze the distribution, uniformity, and other indicators of active pharmaceutical ingredients. Hyperspectral imaging technology overcomes the limitations of Raman hyperspectral point sampling and detecting, and performs wide-band imaging of drugs within a certain field of view, and obtains spectral images of drugs at various wavelengths [67–69]. Figure 7 shows the results of active pharmaceutical ingredients of pharmaceuticals with hyperspectral imaging detecting methods [70, 71]. Kandpal et al., [70] introduce two multivariate data modeling methods for the detection of APIs in finished pharmaceutical products. This method which combines Partial Least Squares Regression (PLSR) and Principal Component Analysis (PCR) technology and benefits from wide-band hyperspectral imaging technology can completely extract the spectral characteristics of the main active ingredients of the drug in the imaging range of 400-2500nm and control the prediction error of the active ingredients of the drug species within 4.45%. Howari et al., [71] focus on the spectroscopic phenomenon of two active pharmaceutical ingredients under the contamination of the drug surface, using a hyperspectral camera to collect qualitative data of the drugs. The results show that this non-destructive, non-polluting, and fast method is helpful for the production, packaging, and quality inspection of drugs. Ktash et al., [72] aimed at the rapid characterization of active ingredients in pharmaceutical tablets, combined with a 225-400nm ultraviolet hyperspectral camera for raw materials such as ibuprofen, acetylsalicylic acid and paracetamol. And principal component analysis method is used to identify the hyperspectral image data of the drugs. This method combines the hyperspectral imaging camera of a specific wavelength band to better extract the ultraviolet spectrum information of the drugs and realizes the rapid characterization of the drug composition with a high accuracy rate, which has great inspiration for the follow-up drug hyperspectral imaging research.

In addition, Sanhueza et al., [73] introduced the application of a confocal laser scanning microscopy hyperspectral imaging technique to identify, locate and quantify the APIs in synthetic tablets. And they used the multivariate curve resolution alternating least squares method (MCR-ALS) to

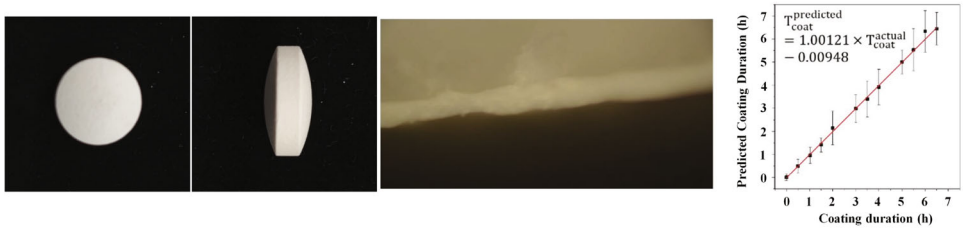

Fig. 6 Detecting the coating thickness of tablets with Raman spectroscopy method [66]. The left figure indicates the optical image of cross-section of the tablet after cleaving and the right diagram indicates the prediction result the drug samples

Table 2 Applications and methods of hyperspectral imaging in pharmaceutical detection

Detection type of pharmaceutical products	Detection content	Detection method
Detection of counterfeit tablets	Antimalarial drug	NIR spectroscopy and PLS-DA [93]
		Raman spectroscopy with PCA and HCA [94]
	antiretroviral drug	NIR chemical imaging and PCA [95]
	drugs for high levels of cholesterol	Raman and NIR spectroscopy with PLS-DA and PCA [96]
	drugs for hypertension disease	NIR chemical imaging and PCA [97]
	drugs for anti-diabetes	NIR spectroscopy with SIMCA and PLS-DA [98]
	Augmentin	multilayer perceptron method with NIR imaging [109]
	Viagra	gray level co-occurrence matrix analysis and PCA [112]
	Drovativarine	SIMCA with NIR spectroscopy [99]
Detecting the content uniformity of tablets	tablets of different batches	Raman chemical imaging with CLS and PCA [100]
		Raman chemical imaging and MCR-ALS [101]
	tablets in the process of manufacturing	NIR chemical imaging with PCA and PLS [102]
		Ripley's K-function and Herfindahl-Hirschman Index [82]
		a method combining HSI and variographic analysis [83]
		PCA and PLSR with NIR imaging [84]
Detecting Multi-morphological tablets	drugs for epilepsy	Raman hyperspectral imaging and MCR-ALS [103]
		Raman spectroscopy and PLS [104]
	drugs for high levels of cholesterol	Raman spectroscopy with MCR-ALS and PLS [105]
	drugs for skin diseases	Raman spectroscopy and PLS [106]
	antifungal drugs	Raman spectroscopy with PCA and PLS [107]
	drugs for headache and fevers	Raman spectroscopy and PLS [108]
Detection of APIs	APIs in finished pharmaceutical products	PLSR and PCR method with visible and NIR imaging [70]
	APIs under contamination surface	PCA with hyperspectral imaging [71]
	rapid characterization of APIs	PCA with hyperspectral imaging [72]
Detection of drug coating thickness and hardness	transdermal drug delivery systems	PLS model with NIR hyperspectral imaging [118]
	acrylic coating	PLS method combined with NIR hyperspectral imaging [119]
	hardness of pharmaceutical tablets	PLSR and PCA method with NIR hyperspectral imaging [120]
Detection of herbal medicine	raw materials and tea bags	PCA and PLS-DA with NIR hyperspectral imaging [125]
	the content of propylene glycol	CARS method based on ELM model [126]
	pectin content in citrus peels	multivariate statistical analysis with NIR hyperspectral imaging [127]

NIR: near-infrared; PLS-DA: partial least-squares to discriminant analysis; PCA: principal component analysis; PLSR: partial least squares regression; SIMCA: soft independent modeling of class analogy; CLS: classical least-squares; UV: Ultraviolent; MCR-ALS: multivariate curve resolution with alternating least-squares; CARS: competitive adaptive reweighted sampling; ELM: extreme learning machine

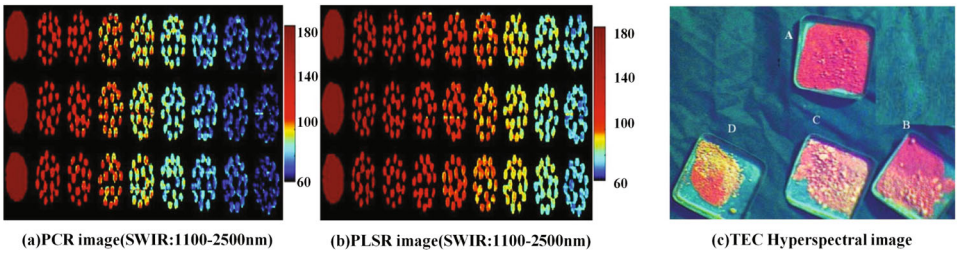

Fig. 7 Analysis of active pharmaceutical ingredients of pharmaceuticals with hyperspectral imaging methods.Picture(a) presents the result of NIR hyperspectral image with PCR method; Picture(b) presents the result of NIR hyperspectral image with PLSR method; Picture(c) presents the result of Tetracycline hydrochloride NIR hyperspectral image

analyze the spectral curve, which could perform qualitative and quantitative analysis of autofluorescent compounds in the presence of interference. Kandpal et al., [74] combined short-wave infrared hyperspectral imaging technology to quickly estimate the content of APIs in powder mixed samples, and established a calibration model of APIs concentration in powder samples using partial least squares (PLS) regression and least square support vector machines (LS-SVM). The results showed that hyperspectral imaging technology could realize the quantification and visualization of pharmaceutical ingredients, and could be conveniently used for non-destructive formulation optimization and product quality control in the production process. Alexandrino et al., [75] aimed at the evaluation of the solid-state stability of pharmaceutical active ingredients and excipients in solid dosage forms during pharmaceutical production and storage, and proposed an evaluation model combined with near-infrared hyperspectral images. The model used the MCR-ALS algorithm to analyze the overlapping compounds during the pixel solid-phase conversion process. The results showed that the inhomogeneity of the drug is prominent, which is of great help to the evaluation of the solid-state stability of the drug. Nishii et al., [76] aimed at the detection of API content and surface coating content in pharmaceutical tablets, and proposed a multivariate data analysis method combined with a near-infrared hyperspectral imaging system. This method could simultaneously determine the active pharmaceutical ingredient content and the coating amount of the tablet with high accuracy. The results show that hyperspectral imaging technology has great prospects for the detection and analysis of pharmaceutical processes.

3.3.2 The Uniformity Detection of the Drug Component Distribution

The uniformity of the drug component distribution in the intermediate product and the finished product is an important factor of pharmaceutical process. Among them, the uneven drug composition will greatly affect the efficacy of the drug and the quality of the drug. Raman hyperspectroscopy cannot obtain the hyperspectral image of the entire tablet at one time during the detection process, so the component analysis application of hyperspectral imaging technology has become a research hotspot [77–81]. Bobiak et al., [82] proposed a Ripley's K-function and Herfindahl-Hirschman Index (HHI) to describe the content of hyperspectral images in response to the problem of ingredient distribution in intermediate and finished pharmaceutical products in the pharmaceutical process. The HHI is calculated by summing the squared scores of the uniformity of all sub-parts in the field of view(FOV). The Ripley's K-function is used to estimate the relative closeness between events. This method effectively solves the application problem of medicinal component analysis in hyperspectral images and provides new ideas for subsequent researchers. Oliveira et al., [83] proposed a new method that combines hyperspectral image and variation analysis in response to the problem of heterogeneity characterization of drugs and analysis of the mixing process of each component of the drugs. As for the samples and blending processes, the new method could provide a qualitative and quantitative description which is suitable for the detection of inhomogeneity and makes it easier to trace the origin of abnormal products. Obisesan et al., [84] proposed principal component analysis and partial least square regression statistical analysis methods for the uniformity detection of chitin lignin nanoparticles (CN-NL). This method combines near-infrared and shortwave infrared hyperspectral imaging of the drugs to obtain the uniformity results of CN-NL on the pullulan substrates. It shows that the hyperspectral imaging combined with chemometrics is a powerful tool for drug uniformity detecting. Alexandrino et al., [85] aimed at evaluating the solid-state stability of APIs and excipients in solid dosage during pharmaceutical production and storage, and proposed an evaluation model combined with near-infrared hyperspectral imaging method. The model uses the multivariate curve resolution alternating least squares method (MCR-ALS) to analyze the overlapping compounds during the pixel solid-phase conversion process. It shows

that the inhomogeneity detecting of the drug is prominent, which is of great help to the evaluation of the solid-state stability of the drugs.

3.3.3 Sorting Detection of Different Types of Tablets

Tablets of the same color but different types often appear in the drug sorting process of pharmaceutical companies. At this time, industrial cameras are not able to distinguish the tablets, and hyperspectral imaging technology is helpful to classify and sort the tablets with the characteristics of different light reflectance on the surface of different drug components [86–89]. Figure 8 shows visualized results of drugs image segmentation and classification. Mazivila et al., [90]. Mazivila et al. [91] carried out experimental research in the process of hyperspectral imaging on the sorting of multi-form tablets. The experiment obtained key information of drug tests including the identification of drugs, the spatial distribution of the APIs of the finished drug, the change of the tablet shape due to inappropriate storage conditions, or the moisture of the excipients, and the change of the solubility of the drug during the crystallization process. The application of related drug detection provides a precedent for hyperspectral imaging detection. Kaneko et al., [88] introduced an infrared hyperspectral detection method to sort pharmaceutical tablets using the nearest neighbor algorithm. In addition, it combines genetic algorithms to select characteristic wavelengths, and finally realizes the sorting of three experimental tablets. This method is simple and practical, and can greatly reduce the cost of hyperspectral detection of drugs, but it may be difficult to apply to the detection of complex and multiple types of pharmaceutical tablets. Liu et al., [90] introduced a convolutional neural network method to analyze near-infrared hyperspectral data and detect the hyperspectral image data of Chinese herbal medicine, coffee beans, and strawberries, achieving 96.72% classification accuracy. Compared with support vector machine, one-dimensional CNN uses the learning weight of the two-dimensional branch in 2BeCNN as an indicator of effective wavelength, and compares it with the successive projection algorithm. The robust detection and sorting effect are achieved with the image characteristics of spectral and spatial dimensions token into account.

3.3.4 Detection of Counterfeit Drugs with Hyperspectral Imaging

In the field of pharmaceutical quality inspection, counterfeit drugs are the focus of government department. Counterfeit drugs will cause irreversible damage to people's life and the healthy development of the pharmaceutical industry. However, most of the current detection methods are invasive and destructive detection methods, such as chemical detection methods and chromatograph detection methods. Not only are the detection speeds slow to achieve mass detection, but they also destroy the appearance of drugs and affect the quality of the products which is harmful to the second sale [92, 109–111]. For the detection of counterfeit drugs, Shinde et al., [109] combined visible and near-infrared hyperspectral imaging equipment and proposed a multi-layer perceptron method. The author distinguishes between genuine and counterfeit drugs by adding calcium carbonate powder to standard drugs and achieved a classification accuracy of more than 90% in the final experimental results. The method is simple and fast and is suit able for quality inspection and authenticity identification of finished pharmaceutical products. However, this method needs to be improved to achieve real market applications in the highly rigorous pharmaceutical market. Wilczyński et al., [112] aimed at the difficulty of detecting counterfeit drugs, and proposed a hyperspectral imaging detection and analysis method to perform gray level co-occurrence matrix analysis (GLCM) and PCA on drug tablets. The results showed that GLCM contrast analysis value of counterfeit drugs is 16% higher than the standard. In addition, the experiment also found that this method could quantitatively analyze the uniformity of the tablet composition, which is of great significance for distinguishing counterfeit drugs from inferior drugs. França et al., [113] aimed at the problem of drug quality control, studied the use of near-infrared hyperspectral cameras to image tablets with different expiration dates, and used the imaging results to evaluate the degradation of captopril

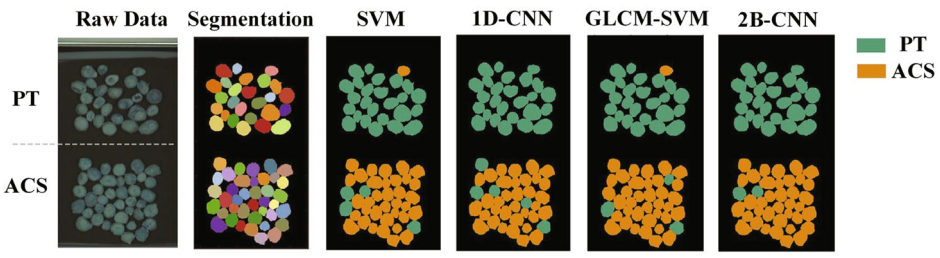

Fig. 8 Visualized results of pinellia ternata and arisaema consanguineum schott images with different methods

on the different layers. The author used the multivariable curve resolution (MCR) model to obtain the concentration distribution maps of the drug which was extracted from the hyperspectral image. Then, a standard model was established to evaluate relationship between the image features and the degradation date of the product to achieve the control of the drug quality. The results show that this method is of great significance for improving safety of drugs and preventing drug degradation.

3.3.5 Detection of Drug Coating Thickness and Hardness

In terms of the detection of drug coating thickness and hardness, hyperspectral imaging technology uses the advantages of wide-band imaging to better detect the thickness and hardness of drug surface coatings [114–117]. Pavurala et al., [118] aimed at the detection of the thickness of the coat of transdermal drug delivery systems, combined with near-infrared hyperspectral imaging technology to obtain the spectral and spatial image information of the coating, and established a Partial least squares (PLS) model to detect coating thickness. The fit of this method reaches 99.33%, and the detection accuracy also reaches 99.33%. The results show that PLS model could detect changes in coating thickness and identify abnormalities such as coating uneven areas and bubbles. Daikos et al., [119] proposed a PLS method combined with near-infrared hyperspectral imaging technology for the detection of the thickness of the acrylic coating on the surface of drugs, and established a calibration model for the drug coating and measured the reference value of thickness conversion under the reflection imaging of infrared spectrum. This method also had an excellent effect in visualizing the spatial distribution of the coating surface and the unevenness of the coating. The results showed that hyperspectral imaging detection had great application prospects in the pharmaceutical process and quality control. Kandpal et al., [120] aimed at the detection of the hardness and the distribution of active ingredients of pharmaceutical tablets, combined with hyperspectral imaging and near-infrared spectroscopy detection technology, and proposed a method combining PLSR and PCA to estimate tablet hardness and visualize the component distribution of samples. This method used the latest spectral imaging technology to solve the problem of non-invasive detection of the mechanical strength of drugs and provided new ways for the hardness detection and active ingredient analysis of pharmaceutical tablets.

3.3.6 Detection of Herbal Medicines

Herbal medicine has received extensive attention from pharmaceutical workers and patients in recent years. Its mild therapeutic effects and unique pharmacological effects have excellent effects in the treatment of many diseases. However, the quality control of herbal medicines has always been a difficult problem. On the one hand, the quality identification of medicinal materials usually relies on manual experience, which is easily interfered by human subjective factors, on the other hand, it is difficult to accurately detect the quality of medicinal materials by machine vision. Hyperspectral imaging technology has natural advantages in herbal medicine detection. Wide-band imaging could accurately detect and analyze herbal medicines of various varieties, origins, and seasons, which brings great convenience to the quality detection of herbal medicines [121–124]. Figure 9 shows herbal medicines analysis using the hyperspectral imaging method [125].

Djokam et al., [125] proposed a PCA principal component analysis method combined with short-wave infrared hyperspectral imaging technology for the quality inspection of medicinal materials such as herbal medicine. This method detected the quality of the 920-2514nm hyperspectral image data of tea raw materials and tea bags, the results of which show that the characteristic spectra of scented teas from different origins were significantly different. In addition, the author also combined the partial least squares discriminant analysis (PLS-DA) method to accurately predicts the raw material composition and proportion of each mixture. This method showed that hyperspectral detection technology, as a reliable, rapid, and non-invasive method, could be used for the identification and ratio analysis of the origin of herbal medicines. Kong et al., [126] aimed

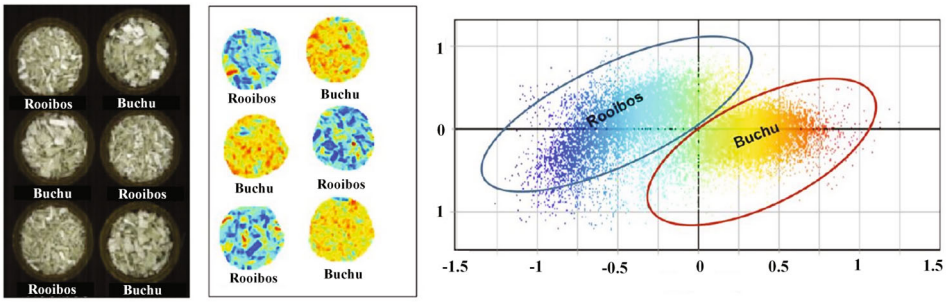

Fig. 9 Herbal medicines analysis using hyperspectral imaging method. And the right diagram illustrate two distinct pixel clusters colored according to score values corresponding to the two teas

at the problem of detecting the content of propylene glycol (MDA) in herbal medicines. They studied a competitive adaptive reweighted sampling (CARS) method based on the extreme learning machine (ELM) model. The experiment combined with PLS method had achieved 92.9% results in the prediction of herbal propylene glycol content. The results showed that hyperspectral imaging technology had huge advantages in the detection of propylene glycol content in herbal medicines, and its non-invasive and rapid detection process was suitable for the qualitative detection of industrial drugs. Badaró et al., [127] aimed at the analysis of pectin content in citrus peels, and used multivariate statistical analysis combined with short-wave infrared hyperspectral images in the 900-2500nm band to analyze the pectin content of different types of citrus peels. In terms of detection accuracy, PLSR method based on the full spectrum has high accuracy (92%-94%). Results. In addition, the surface shortwave infrared hyperspectral imaging technology had considerable potential in the quantitative analysis of the content of pectin in the peel. As a fast, non-invasive new detection method, hyperspectral detection and analysis technology has the incomparable advantages of chemical detection methods.

3.4 Machine Vision Applications for Hyperspectral Images

As a kind of digital image, hyperspectral image data is characterized by more spatial data of spectral dimension in data dimension. Therefore, in the face of hyperspectral image data with surging data volume, general method with strong selection feature extraction ability and good generalization performance is a hot topic in current research [128–131]. Deep learning is recognized as a powerful feature extraction method and a method to deal with nonlinear problems. Its research in image processing covers all levels of natural science, so it also has rich reference significance in the processing of medical hyperspectral data [132, 133].

In the early study of hyperspectral image processing, there are many pixel level methods, such as neural network [134], support vector machine [135], polynomial logistic regression [136, 137] and so on. These methods are mainly applied to the classification and detection of hyperspectral images, such as drug sorting, counterfeit drug detection and so on. With the deepening of relevant studies, the feature extraction capability of network has attracted the attention of researchers. Therefore, in terms of the design of convolution kernel, For example, composite kernel [138] and moldova kernel [139, 140] and other designs focusing on image feature extraction ability are gradually popular in this field. However, the prominent feature of hyperspectral images lies in the strong correlation between spectral images. Therefore, Liu [141] et al.,proposed a method based on active learning, which has a strong ability to extract spectral features of hyperspectral images. In addition, Zhong [142] et al., also proposed an improved method. The precision of image classification is improved by fine-tuning the pre-training model. In the aspect of network design of spectral feature extraction, there are 1-d CNN [143–146], 1-d GAN [147, 148] and RNN [146, 149, 150], etc. These researches bring new ideas to the processing of medical hyperspectral images.

4 Challenge and Perspective

Immunologists typically use the number of fluorescent immune cell footprints or spot-forming cells to assess the immune response and the protection the vaccine provides when evaluating indicators such as the effectiveness of a vaccine product. In addition, the imaging and counting of T cells and other immune cells can not be separated from the support of hyperspectral technology. [151–154]. At present, due to the limitation of spectral imaging technology, imaging detection and analysis of immunoglobulin and other immunoactive molecules cannot be applied and promoted at the industrial level for the time being. However, it is believed that hyperspectral technology will play a unique role in the detection and application of vaccine products with the breakthrough of technology in the near future.

At present, the application of hyperspectral technology in the pharmaceutical field is still limited to the fields of active drug component detection, drug authenticity identification, drug component analysis, and drug coating thickness detection. Drug detection methods are mostly concentrated in principal component analysis (PCA), with partial minimum In terms of statistical analysis methods such as quadratic regression (PLSR), the application scenario is generally to do sample testing in the laboratory, and it has not been extended to industrial pharmaceutical production lines and other places. Therefore, the current application prospects of hyperspectral technology in the field of pharmaceutical testing are broad, but the challenges are huge. How to implement the application of hyperspectral technology in pharmaceutical detection in the industrial pharmacy scene with high precision and low cost is the biggest challenge at present. The lack of pharmaceutical hyperspectral data sets and insufficient research enthusiasm are important factors restricting the further development of this technology. Therefore, researchers not only need to expand from detection methods to commonly used methods of machine vision but more importantly, they need to continuously introduce common pharmaceutical detection

data sets to support the continuous progress of hyperspectral technology in this field.

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Declarations

Conflict of Interests The authors declare no conflict of interest.

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