Monitoring drug quality in the circulation field using NIR spectral rapid comparison methods

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Keywords: NIR; Conformity test; Correlation coefficient method; Monitor; Drug quality

Introduction

The spread of counterfeit drugs is a major problem all over the world. Analysts have used near-infrared (NIR) spectroscopy to identify counterfeit drugs since 2001.[1–5] A NIR drug pre-screening system was constructed by NICPBP in 2004, which contained universal models that can identify and quantify a given drug with the same API (active pharmaceutical ingredients) made by different manufacturers all over China.[6,7] Now the system has been equipped in mobile labs for rapidly screening drug quality on-site.[8]

Construction of a universal model is time-consuming, and is restricted by sample collection and model optimization. When a new counterfeit drug is found in the market, it is difficult to construct a universal model for such a drug immediately. Furthermore, the universal models can't be used for identifying the drug imitations and the chemicals illegally added in traditional Chinese Medicine (TCM).

Since 2006, we have attempted to use spectral rapid comparison models to compensate for the weakness of universal models. As shown in Figure 1., all these models build up our new NIR screening system. Four such methods and their applications are introduced in this paper.

Experimental

Apparatus and software

The FT-NIR spectrometers, MATRIX-F from Bruker (Bruker Optics, Suite 5123, Zhong Guan Cun South Street, Beijing 100081, China) were used to collect diffuse reflectance spectra. Bruker OPUS software was used for data analysis.

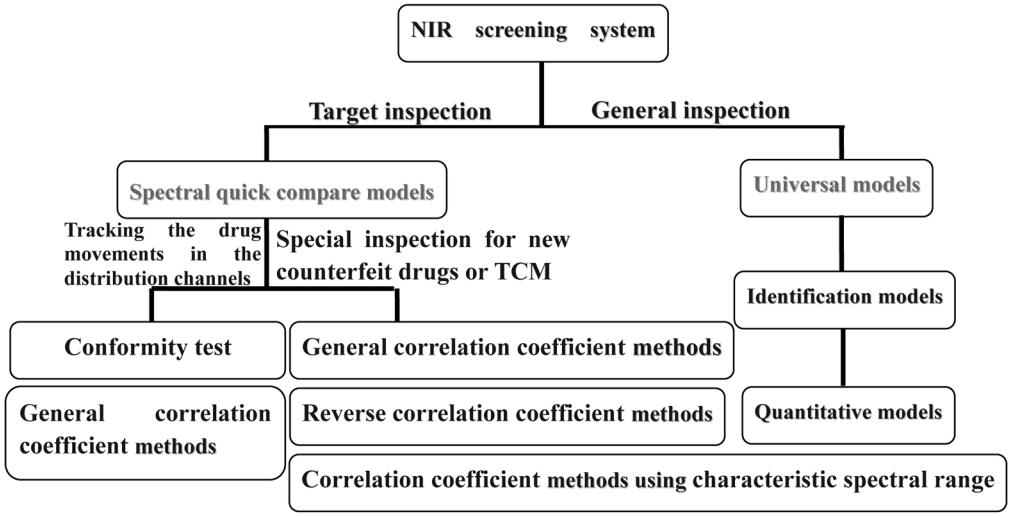

Figure 1. Scheme of NIR screening system in mobile labs.

Samples

39 batches of Lijunsha® (erythromycin ethylsuccinate tablets) were supplied by Xi'an Lijun Pharmaceutical Co., Ltd, Other drugs were retention samples of NICPBP. All the samples were demonstrated using the legally official laboratory method.

Spectral rapid comparison methods

Conformity test

The NIR spectra of 30 samples for each batch of Lijunsha® are recorded as the reference. The mean value plus/minus 5 times the σ for each wave-number determined the confidence band within the spectral range of 4000–10000 cm^{-1}, and first derivative and vector normalization were the pre-processing methods. The conformity test models for each batch of Lijunsha® were constructed using this method. If the max CI (Conformity Index) of the tested sample is greater than 5, the sample will be regarded as a suspected drug.

$$CI = (A_{reference,i} - A_{sample,i}) \div \sigma_{reference,i}$$

Ai = the Absorbance at wave-number i

$\sigma_{reference,i}$ = the standard deviation of absorbance at wave-number i for reference samples

General correlation coefficient method

When a new counterfeit drug appears in one pharmacy, using the spectrum of its corresponding authentic drug as the reference, and the second derivative and vector normalization as the pre-processing methods, the correlation coefficient model is constructed, to quickly inspect this kind of drug in other pharmacies nearby. The spectral regions are 6200–5500 cm^{-1}, 5000–4700 cm^{-1}

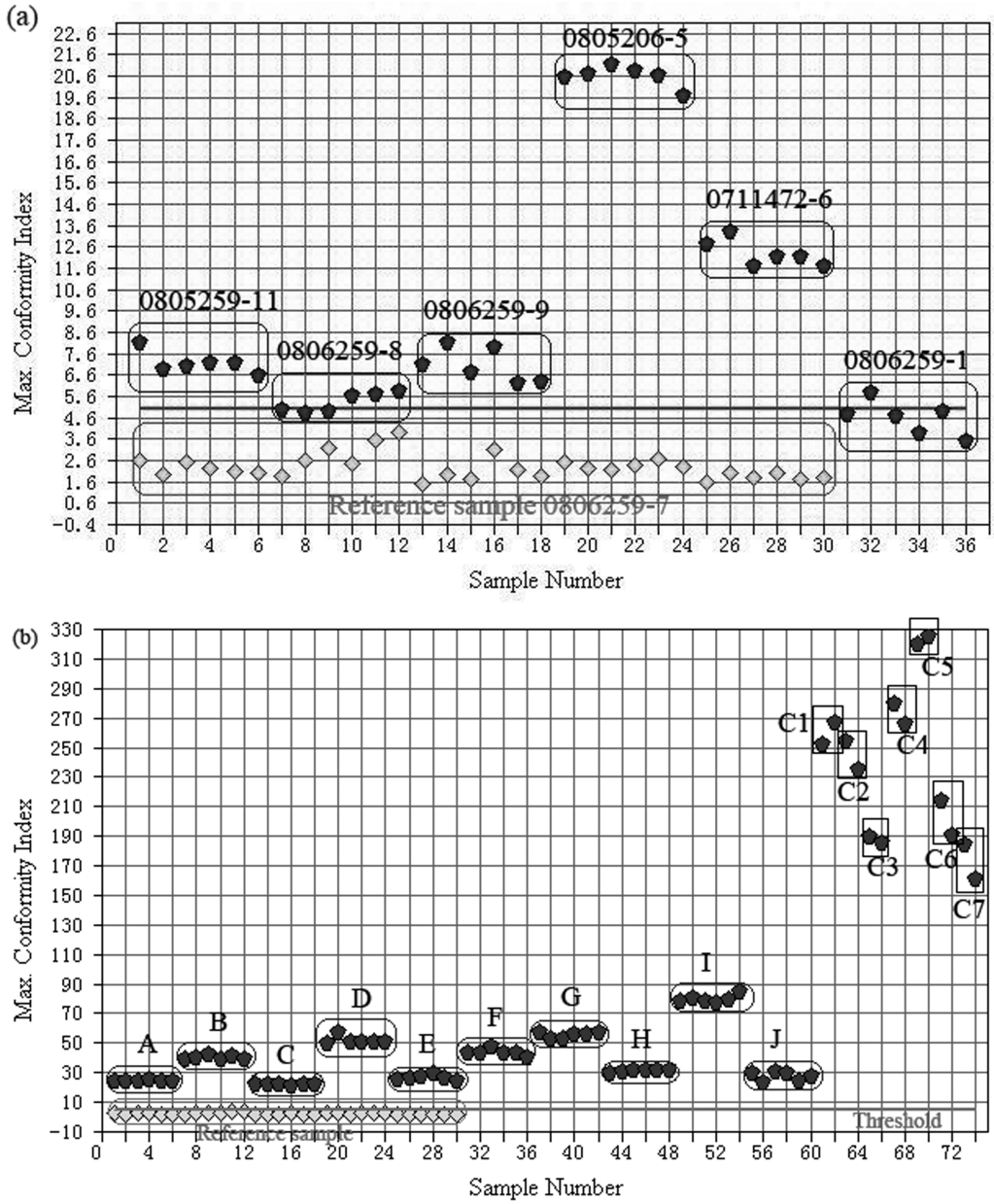

Figure 2. Distribution of the max CI for erythromycin ethylsuccinate tablets from different batches of Lijunsha® (a), other manufacturers except Lijun and counterfeit drugs (b).
(The number group in Figure 2a represents batch number. A-J represent different manufacturers, C1-C7 represent 7 batches of counterfeit drugs.)

and 7240–7140 cm^{-1}, which have been proved to be sensitive to the change of API and excipients. The initial threshold has been set as 95 % based on the experiments. If r between the reference and the tested spectra is less than 95 %, the tested sample will be regarded as a suspected drug.

$$r = \frac{Cov(y_1(k), y_2(k))}{\sigma_{y1} \cdot \sigma_{y2}}$$

$Cov(y_1(k), y_2(k))$ = The covariance of Spectra $y_1(k)$ and $y_2(k)$.
σ = The standard deviation.

Reverse correlation coefficient method

The chemical illegally added in TCM is a common kind of counterfeit drug in China. We proposed using the added chemical as the reference sample to calculate the correlation coefficient between the reference and the tested spectra. The regions and pre-processing methods are the same as that in the previous section. The threshold was set based on the minimum effective concentration of that chemical. If r is greater than the threshold, the tested sample will be suspected to contain that chemical. We defined this method as reverse correlation coefficient method.

Correlation coefficient method using characteristic spectral ranges[9]

If some characteristic spectral regions of the added chemical are not affected by the components of the TCM, one can set up a reverse correlation coefficient model using such ranges. This approach is called the correlation coefficient method using characteristic spectral ranges.

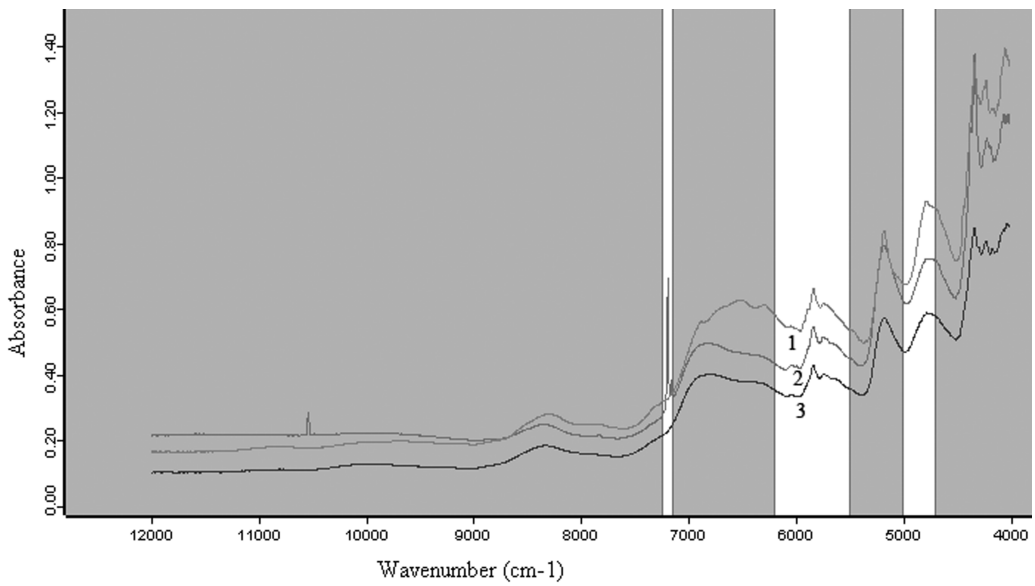

Figure 3. Reflectance spectra for Motilium® (1), counterfeit Motilium® without API (2) and the imitation with API (3) through blister package.

Results and discussion

Tracking the distribution of Lijunsha®

The specificity of the conformity test for each batch of Lijunsha® was evaluated by the erythromycin ethylsuccinate tablets from different batches of Lijunsha®, other manufacturers except Lijun, and counterfeit drugs. As shown in Figure 2, the max CI of these samples had obvious differences compared with that of the reference samples.

Up until now 6,500,000 samples of 39 batches of Lijunsha® which were sold to Henan, Hubei and Anhui Provinces, have been tracked, using their corresponding conformity test models equipped in mobile labs. Most of them were inspected at community hospitals or pharmacies in cities, and 3 batches were checked at the pharmacies in rural areas. Tracking results showed that the maximum circulation time was 8 months. Only 4 samples were identified incorrectly. The results indicate that it is feasible to use the conformity test to track drug movements in the circulation field, to prevent the authentic drugs from being illegally substituted by counterfeit ones.

Rapid inspection of new counterfeit drugs

The correlation coefficients of 14 batches of counterfeit drugs and their corresponding authentic drugs were calculated, using the general correlation coefficient method. All of the correlation coefficients were less than 95 %, which indicated that the initial threshold is suitable.

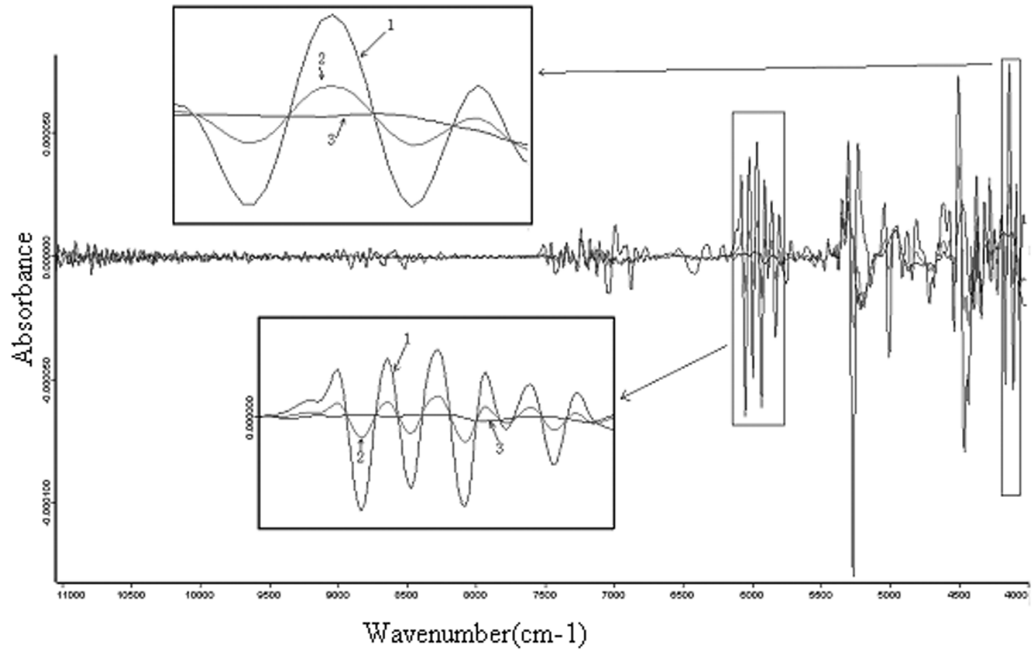

Figure 4. Reflectance spectra for the reference substance of sildenafil citrate (1); the capsule of the TCM with illegal added sildenafil citrate (2); the authentic capsule of the TCM for erectile dysfunction (second derivative after 13 points smoothing followed by vector normalization).

From 2006 to 2008, 32 batches of counterfeit drugs were found, using the general correlation coefficient method in the mobile lab at Shangqiu, Henan Province. As Figure 3 shows, the spectra of authentic and counterfeit drugs have obvious differences in the selected regions.

Detecting the chemicals illegally added in the TCM

When detecting whether metformin hydrochloride is illegally added in capsules of the TCM for antidiabetic conditions, 20 batches were screened using the reverse correlation coefficient method. The accuracy was 100 %.

When using this method to screen the illegal addition of sildenafil citrate, the TCM for erectile dysfunction, 466 batches of capsules were tested. The accuracy was 89.17 %.

In the regions of 6070–5800 cm^{-1} and 4170–4070 cm^{-1} (Figure 4), the counterfeit TCM with sildenafil citrate has considerable similarity to the sildenafil citrate reference substance. The reverse correlation coefficient model, using these spectral regions was set up. When using this model in mobile labs, 244 batches of TCM were screened and the accuracy was 93.4 %.[9]

Conclusion

In summary, these four spectral rapid comparison methods can be constructed relatively easily for monitoring drugs quality on-site, with acceptable accuracy.

References

1. S.H.F. Scafi and C. Pasquini, *Analyst* **126,** 2218 (2001).
2. B.A. Olsen, M.W. Borer, F.M. Perry and R.A. Forbes, *Pharmaceut. Technol.* **26,** 62 (2002).
3. O. Ye. Rodionova, L.P. Houmøller, A.L. Pomerantsev, P. Geladi, J. Burger, V. L. Dorofeyev and A.P. Arzamastsev, *Anal. Chim. Acta* **549,** 151 (2005).
4. M.J. Vredenbregt, L. Blok-Tip, R. Hoogerbrugge, D.M. Barends and D. De Kaste, *J. Pharm. Biomed. Anal.* **40,** 840 (2006).
5. F.E. Dowell, E.B. Maghirang, F.M. Fernandez, P.N. Newton and M.D. Green, *J. Pharm. Biomed. Anal.* **48,** 1011 (2008).
6. Y.C. Feng and C.Q. Hu, *J. Pharm. Biomed. Anal.* **41,** 373 (2006).
7. Y.C. Feng, X.B. Zhang and C.Q. Hu, *J. Pharm. Biomed. Anal.* **51,** 12 (2010).
8. R. Mukhopadhyay, *Anal. Chem.* **79,** 2622 (2007).
9. X.L. Wang, Y.C. Feng, C.Q. Hu, *Chin. J. Anal. Chem.* (2009) in press.