Survey to Identify Substandard and Falsified Tablets in Several Asian Countries with Pharmacopeial Quality Control Tests and Principal Component Analysis of Handheld Raman Spectroscopy.

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Survey to Identify Substandard and Falsified Tablets in Several Asian Countries with Pharmacopeial Quality Control Tests and Principal Component Analysis of Handheld Raman Spectroscopy

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Abstract. The World Health Organization has warned that substandard and falsified medical products (SFs) can harm patients and fail to treat the diseases for which they were intended, and they affect every region of the world, leading to loss of confidence in medicines, health-care providers, and health systems. Therefore, development of analytical procedures to detect SFs is extremely important. In this study, we investigated the quality of pharmaceutical tablets containing the antihypertensive candesartan cilexetil, collected in China, Indonesia, Japan, and Myanmar, using the Japanese pharmacopeial analytical procedures for quality control, together with principal component analysis (PCA) of Raman spectrum obtained with handheld Raman spectrometer. Some samples showed delayed dissolution and failed to meet the pharmacopeial specification, whereas others failed the assay test. These products appeared to be substandard. Principal component analysis showed that all Raman spectra could be explained in terms of two components: the amount of the active pharmaceutical ingredient and the kinds of excipients. Principal component analysis score plot indicated one substandard, and the falsified tablets have similar principal components in Raman spectra, in contrast to authentic products. The locations of samples within the PCA score plot varied according to the source country, suggesting that manufacturers in different countries use different excipients. Our results indicate that the handheld Raman device will be useful for detection of SFs in the field. Principal component analysis of that Raman data clarify the difference in chemical properties between good quality products and SFs that circulate in the Asian market.

INTRODUCTION

In May 2017, definition of substandard and falsified medical products (SFs) was announced by the World Health Organization.[1] Substandard medical products (also called "out of specification") are authorized by national regulatory authorities but fail to meet either national or international quality standards or specifications, or in some cases, both. On the other hand, falsified medical products deliberately or fraudulently misrepresent their identity, composition, or source.[1–5] Many surveys of falsified medical products and analytical procedures for investigation of the authenticity of medical products have been reported by various public institutes.[2–12] In 2015, the Pharmaceutical Security Research Institute reported that Asia experienced the highest incidence of drug crime cases among seven regions in the world. In that year, a total of 3,002 cases of drug crime cases were recorded, among which around 1,000 involved the Asia-Pacific region.[13] Many cases where defective products have been transported across national borders have been reported.[14]

Relatively little work has been carried out on analytical methods for investigating the actual status of substandard medical products, including their distribution, and their physical and chemical properties.[14,15] One reason for this maybe concern about the possibility of excessively hindering the development of medicines and access to medicines in developing countries.[16] Also, regular quality control and surveillance of medicines after marketing tend to be more difficult in developing countries for various reasons, including high cost, the need for sophisticated equipment and skilled technicians, and lack of pharmacological knowledge to recognize the need for implementation of countermeasures.[6,15,17–19] Furthermore, medicines may be transported across national borders without proper quality checks through various distribution channels.[14,20] These are serious issues to be taken measure of, because SFs can cause treatment failure, development of antimicrobial resistance, and serious adverse drug reactions, thereby damaging public confidence in medicines.[2,21,22]

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q6A provides guidance to establish a harmonized set of global specifications consisting of analytical procedures and acceptance criteria for new drug substances (DS) and drug products (DP) for human use (1999).[23] Specifications of DS and DP are proposed and justified by the manufacturer, and approved by regulatory authorities in each country. The specifications and acceptance criteria are focused on those chemical, physical, and biological properties considered to be important for ensuring the safety and efficacy of DS and DP. Thus, they can be adopted to identify substandard products. Possible issues include 1) out-of-specification content of active pharmaceutical ingredient (API),[24,25] 2) significant dissolution delay,[24] 3) contamination with toxic substances,[26,27] and 4) lack of sterility.[28,29] These points can be checked by means of assay, content uniformity testing, measurements of dissolution properties and impurities, and microbial tests.

In this study, candesartan cilexetil tablets were collected in China, Indonesia, Japan, and Myanmar and subjected to quality control tests (assays, content uniformity, and dissolution tests) according to the Japanese pharmacopeia.[30] The acceptance criteria for these tests in the Japanese pharmacopeia were adopted as thresholds for identification of SFs.

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TABLE 1
Summary of collected samples from China, Indonesia, and Myanmar

No.	Product name stated on the package	Dose (mg)	Manufacturing country printed on package	Sampling area	Sampling year	Sampling facility
1–7	Blopress	8	Japan	Shanghai, China	2012	Hospital 1–7
8–9	悉君宁	4	China	Shanghai, China	2012	Hospital 8–9
10–11, 13	维尔亚	8	China	Shanghai, China	2012	Hospital 10–11, 13
12	维尔亚	4	China	Shanghai, China	2012	Hospital 12
14–26	XINXIN	4	China	Shanghai, China	2012	Hospital 14–26
27–30	Candelong-8	8	India	Mandalay, Myanmar	2015	Pharmacy A–D
31–33	Advant	8	Pakistan	Mandalay, Myanmar	2015	Pharmacy E–G
34	Falsified product imitating Blopress	16	Indonesia	Medan, Indonesia	2009	Pharmacy H
35, 37	Falsified product imitating Blopress	16	Indonesia	Jakarta, Indonesia	2011–2012	Pharmacy I, J
36	Falsified product imitating Blopress	8	Indonesia	Jakarta, Indonesia	2011	Pharmacy I

Many issues of quality and bioavailability are considered to be due to technical deficiencies in the manufacturing process design and differences in the nature of the excipients.[31–33] Although many studies have shown that excipients influence quality, the excipients are not generally stipulated in quality tests. Our previous study found that the types of the excipients used in candesartan cilexetil tablets differ depending on the manufacturer, and Raman spectra of the tablets showed the different pattern reflecting the chemical nature of the excipients.[34] Here, we focused on the methodology for detecting substandard and falsified medicines by principal component analysis (PCA)[12,22,35–43] of raw data obtained by handheld Raman spectroscopy. We aimed to clarify the chemical features of substandard medicines by comparing them with authentic medicines, and by extracting the principal components of the Raman spectrum to visualize the relationships among the tablets. We chose the handheld Raman device as a simple spectroscope suitable for in situ observation in developing countries, and we used PCA as a mean to extract critical information despite the limited resolution and sensitivity of the device. We also compared signal preprocessing methods of Raman spectra for PCA and selected the multiplicative scattering correlation (MSC) method as being particularly suitable to extract the desired signals from the

TABLE 2
Summary results of the assay, content uniformity and dissolution tests of candesartan cilexetil tablets, and chemical similarity based on Raman spectra

			Dissolution				Assay				
No.	Stated product name	Dose (mg)	Mean of dissolution rate (%)	Standard deviation	Number of tablets	Judgment	Mean of content (%)	Standard deviation	Number of tablets	Judgment	Chemical similarity by Raman spectra
1	Blopress	8	99	1.9	3	Pass	103.9	0.4	3	Pass	0.7159
2	Blopress	8	86	0.6	3	Pass	102.7	3.3	3	Pass	0.5689
3	Blopress	8	95	0.4	3	Pass	104.0	0.4	3	Pass	0.6546
4	Blopress	8	95	0.4	3	Pass	100.5	0.1	3	Pass	0.6914
5	Blopress	8	93	2.2	2	Pass	101.2	0.6	3	Pass	0.6763
6	Blopress	8	90	1.8	3	Pass	99.9	0.7	3	Pass	0.5910
7	Blopress	8	88	1.3	3	Pass	101.1	1.7	3	Pass	0.6158
8	悉君宁	4	84	0.6	3	Pass	94.4	2.2	3	Fail	0.0000
9	悉君宁	4	86	3.1	3	Pass	94.4	2.1	3	Fail	0.0000
10	维尔亚	8	83	1.5	3	Pass	100.9	1.5	3	Pass	0.0000
11	维尔亚	8	81	4.1	3	Pass	103.5	4.8	3	Pass	0.0000
12	维尔亚	4	84	0.2	3	Pass	97.7	0.6	3	Pass	0.1483
13	维尔亚	8	81	4.0	3	Pass	103.7	0.8	3	Pass	0.0000
14	XINXIN	4	68	15.9	3	Fail	109.1	1.6	3	Fail	0.0000
15	XINXIN	4	88	3.8	3	Pass	108.7	1.8	3	Fail	0.0000
16	XINXIN	4	90	4.1	3	Pass	107.4	2.1	3	Fail	0.0000
17	XINXIN	4	85	1.0	3	Pass	104.4	2.5	3	Pass	0.0000
18	XINXIN	4	91	0.2	3	Pass	109.0	2.7	3	Fail	0.0000
19	XINXIN	4	90	4.4	3	Pass	110.3	0.4	3	Fail	0.0000
20	XINXIN	4	87	4.4	3	Pass	111.7	1.2	3	Fail	0.0000
21	XINXIN	4	83	1.2	3	Pass	107.2	4.8	3	Fail	0.0000
22	XINXIN	4	82	1.2	3	Pass	106.5	2.5	3	Fail	0.0000
23	XINXIN	4	89	3.1	3	Pass	105.1	1.8	3	Fail	0.0000
24	XINXIN	4	92	0.1	3	Pass	109.0	1.1	3	Fail	0.0000
25	XINXIN	4	63	13.3	3	Fail	112.8	4.0	3	Fail	0.0000
26	XINXIN	4	88	0.9	3	Pass	110.4	1.8	3	Fail	0.0000
27	Candelong-8	8	104	0.4	6	Pass	102.0	1.2	10	Pass	0.0337
28	Candelong-8	8	106	0.2	3	Pass	103.0	0.3	3	Pass	0.0969
29	Candelong-8	8	103	2.9	6	Pass	100.6	2.2	10	Pass	0.0457
30	Candelong-8	8	103	1.1	6	Pass	101.4	2.1	10	Pass	0.0302
31	Advant	8	95	2.9	6	Pass	93.3	3.8	10	Fail	0.1725
32	Advant	8	90	0.1	3	Pass	101.0	1.9	3	Pass	0.2416
33	Advant	8	92	1.8	6	Pass	97.0	3.0	10	Pass	0.1421

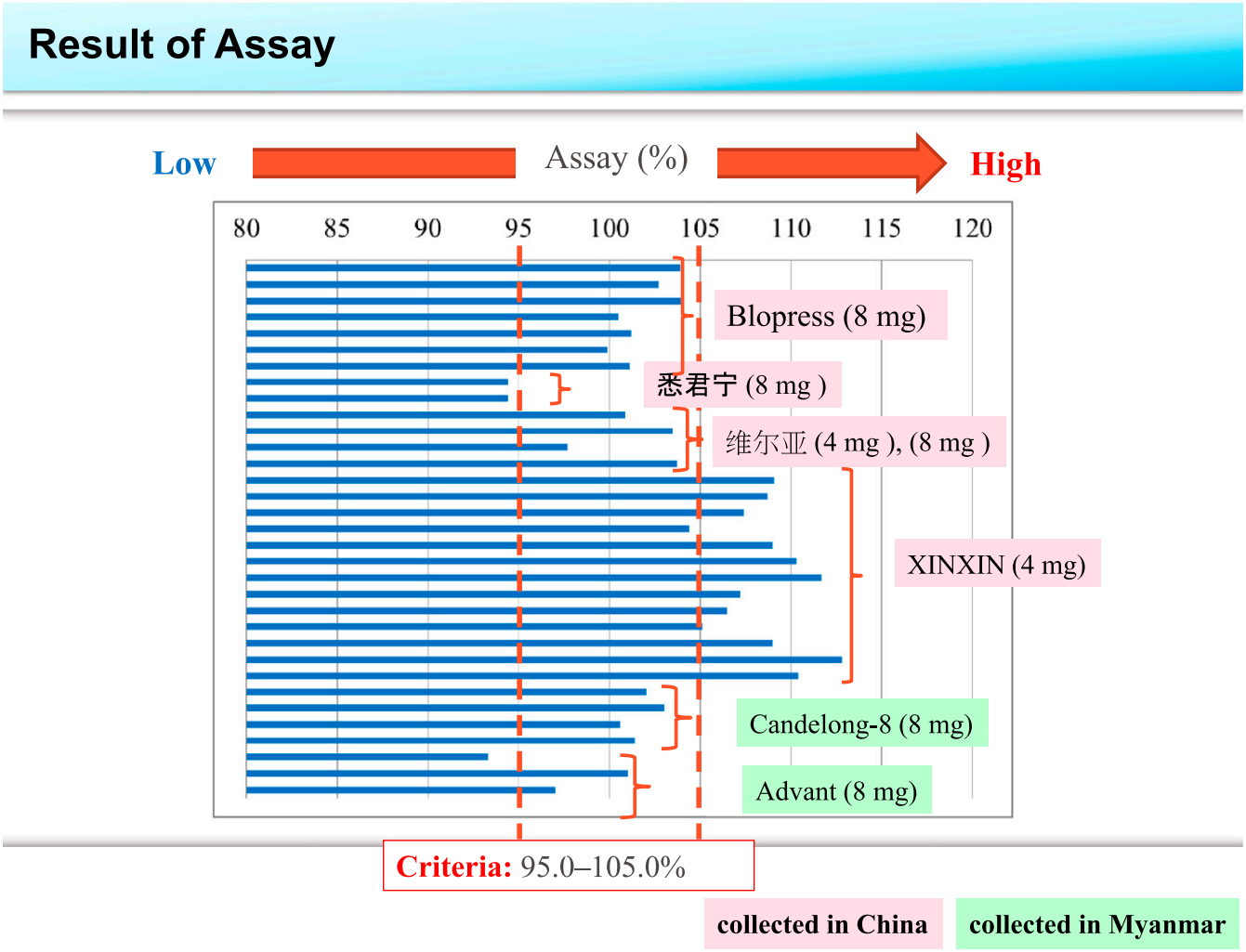

FIGURE 1. Comparison of assay for the samples collected in China and Myanmar. Two vertical dashed lines show the acceptance criteria of 95.0–105.0% assay. This figure appears in color at www.ajtmh.org.

strong fluorescence background.[43] This approach proved highly effective to evaluate the degree of similarity among samples.

EXPERIMENTAL

Sample collection. Authentic candesartan cilexetil tablets (Blopress 4 mg, 8 mg and 12 mg) and placebo tablets including the excipients same as Blopress except API were supplied by a Japanese manufacturer (Takeda Pharmaceutical Company Ltd., Osaka, Japan) as the reference samples. Samples of candesartan cilexetil tablets were collected from the hospitals and clinics in China, Indonesia, and Myanmar and also purchased via the internet (2009–2015). The falsified products imitating Blopress discovered in Indonesia have been reported to Forensics, Brand Protection, and Investigations. These falsified products were identified based on visual inspection of the packaging.[34]

Visual inspection. First, we observed the outer package and package insert, Press Through Pack, or aluminum blister packaging. The product name, dose, component, formulation, packaging unit, manufacturer, manufacturing date, expiration date, and manufacturing number were recorded. The cartons were examined visually and microscopically and compared with reference samples. Printing on the edge of the tape seal was carefully observed to check fine details.

Quality control test. Content uniformity,[44] assay, and dissolution tests of candesartan cilexetil tablets were conducted according to Japanese pharmacopeia.[30]

Acetonitrile (for high-performance liquid chromatography [HPLC]), polyoxyethylene 20, and sorbitan monolaurate (for biochemistry) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), acetic acid, and acenaphthene were purchased from Nacalai Tesque Co., Ltd (Kyoto, Japan).

Content uniformity and assay. Candesartan cilexetil in tablets were extracted in a mixture of acetonitrile and water (3:2) and measurements were carried out at a wavelength of 305 nm using a spectrophotometer (U-3210, HITACHI, Tokyo, Japan). Because the number of the collected samples was limited, two, three, or 10 tablets were used for each evaluation of content uniformity and the mean of the content was calculated as the result for assay. The acceptance criterion for the assay was set to 95.0–105.0% as same as the criterion in Japanese Pharmacopeia.[30]

Dissolution. The dissolution test was performed under the condition described for Apparatus 2 (paddle method) with 50-rpm agitation in 900 mL of a dissolution medium containing

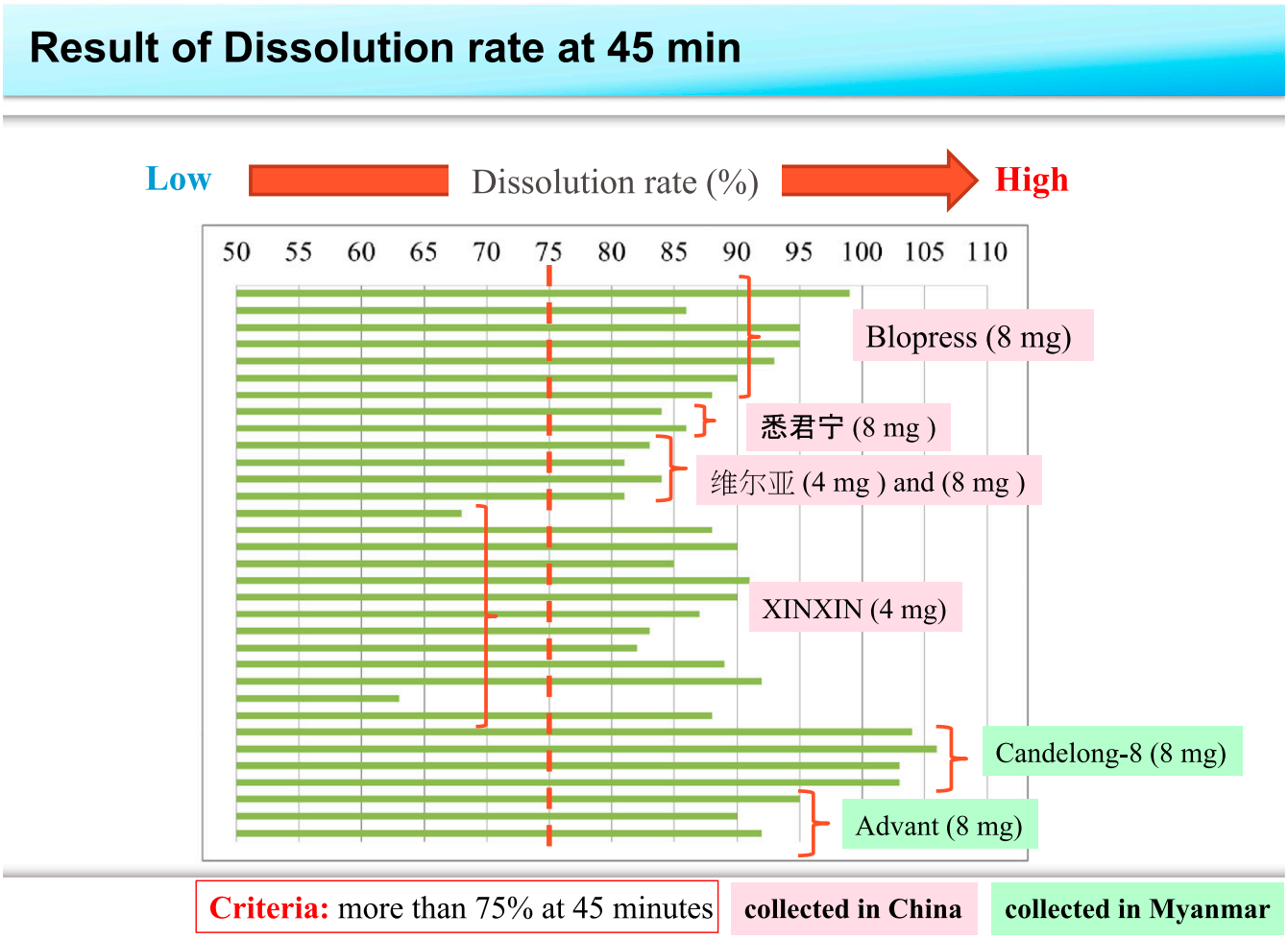

FIGURE 2. Comparison of dissolution rate (%) for the samples collected in China and Myanmar. The vertical dashed line shows the acceptance criteria should be more than 75% dissolution rate at 45-minute sampling time. This figure appears in color at www.ajtmh.org.

10 w/v% polyoxyethylene (20) sorbitan monolaurate at 37°C. A sample was taken at the time point of 45 minutes, and examined by high-speed liquid chromatography (HPLC, L-7200 autosampler, D-7000 interface, L-7100 pump, L-7300 column, L-7405 UV detector, HITACHI, Tokyo, Japan). Acenaphthene was added to the test solution as the internal standard. High-performance liquid chromatography conditions were as follows: 5-μm-octa decyl silyl (ODS) column (Shim-pack CLC-ODS (M) 15 cm, SHIMADZU, Kyoto, Japan), a flow rate of 1.8 mL/minute, a column temperature of 25°C, an injection volume of 50 μL, a detection wavelength of 254 nm. The mobile phase was a mixture of acetonitrile, water, and acetic acid (57:43:1). The mean of the dissolution rate of two, three, or six tablets were evaluated, respectively. The criterion was set that the dissolution rate of candesartan cilexetil should be more than 75% at the 45-minute sampling point.[30]

Handheld Raman spectroscopy. All tablets were examined with a handheld Raman spectrometer (TruScan®, Thermo Fisher Scientific, Waltham, MA). The chemical equivalence between the authentic reference product (tablets containing 8 mg API) and the collected samples was evaluated based on the *P* value for similarity of the Raman spectra, which was automatically calculated by the instrument's built-in algorithm, which has been validated, but not disclosed, and is designed not to be modified. Next, the raw Raman data were subjected to PCA analysis. Spectra components from the API were obtained by analysis of authentic tablets containing 0 mg (Placebo), 4 mg, 8 mg, and 12 mg of the API. The weight and size of 0 mg (Placebo), 4 mg, 8 mg, and 12 mg tablets are equivalent, and same weights of each excipient except lactose monohydrate to adjust total weights of them.

Preprocessing of Raman spectra. The data interval of the handheld device is around 1.4–2.2 cm^{-1} and the noise level is high, so preprocessing of the spectroscopy spectra is critical for accurate PCA calculation. We used the Savitzky–Golay (SG) method[45] to smooth each segment of the original Raman spectrum in a small window by fitting to a polynomial function.[45,46] The MSC method[46–49] was also applied to eliminate the baseline shift caused by the multiplication of the baseline tilts and the additive shift of the baseline shifts up and down.[46–49] Multiplicative scattering correlation can use data from many wavelengths to distinguish between light absorption and light scattering, correcting spectra according to a simple linear univariate fit to a standard spectrum by means of least-squares regression using the standard spectrum.[47] The observed spectrum $Y(\omega)$ is considered to depend on wavelength as follows:

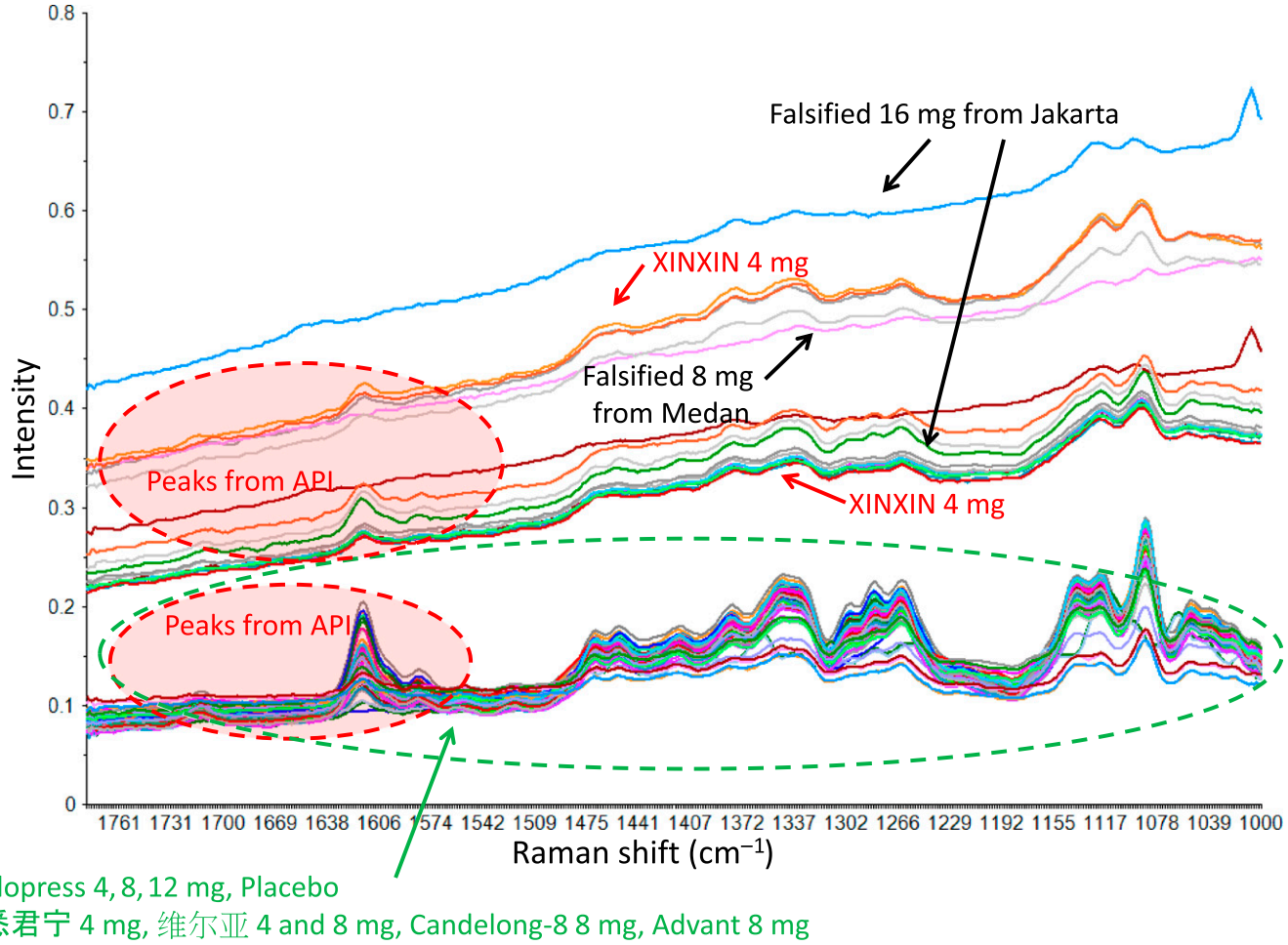

FIGURE 3. Raman spectra of candesartan cilexcetil tablets and the falsified products (before multiplicative scattering correlation preprocessing of Raman spectra). This figure appears in color at www.ajtmh.org.

$$Y(\omega) = \overline{Y(\omega)} + a\omega + b + e(\omega), \quad (1.1)$$

where, $\overline{Y(\omega)}$ is the standard spectrum and $e(\omega)$ represents the residual. a and b are adjusted to minimize the term of $e(\omega)$, to make these discrete deviations as small as possible.[47]

Principal component analysis. The Unscrambler® X software (CAMO Software, Oslo, Norway) was used for PCA. The Raman spectra data set consisting of 85 samples and 476 wavenumbers was calculated and it was decomposed into a linear combination of score t_n and loading p_n consisting of several principal components, allowing the spectrum to be understood clearly with a limited number of principal components. That is, the data set X is decomposed into a linear combination of the score and the loading as shown in equation (1.2).

$$X = t_1p_1 + t_2p_2 + t_3p_3 + \cdots t_Np_N \quad (1.2)$$

The validity and robustness of the calculated PCA model were confirmed by cross-random validation.

RESULTS

Table 1 shows the summary of collected samples from China, Indonesia, and Myanmar. More than 15 brands of candesartan cilexetil tablets are available in China, as judged from an internet survey, but only four were found to be distributed in hospitals and clinics in Shanghai. The products distributed in Shanghai in China were from manufacturers in China and Japan. On the other hand, three brands, manufactured in Japan, India, and Pakistan, were found in private hospitals, community pharmacies, and wholesalers in Mandalay, Myanmar. No obvious deficiencies in the PTP packaging, package insert for use, pillows, or tablets were found in visual inspection of all collected samples.

Content uniformity, assay and dissolution. Table 2 summarizes the results of the content uniformity, assay, and dissolution tests of collected samples. The assay values of 12 of 13 samples of the tablets stated as XINXIN candesartan cilexetil tablets exceeded the upper limit of 105.0%. Two samples stated as 悉君宁 and one sample stated as Advant candesartan cilexetil tablets gave an assay value less than the lower acceptance limit of 95.0% as shown in Figure 1. Dissolution delay was confirmed in two samples of XINXIN candesartan cilexetil tablets, which failed to meet the criterion dissolution rate of more than 75% at 45 minutes as shown in Figure 2. Other tablets met the criterion.

Handheld Raman spectroscopy and PCA. Raman spectra obtained with the handheld instrument are shown in Figure 3. The spectral features are mainly due to the API and the excipients, including lactose monohydrate. The Raman

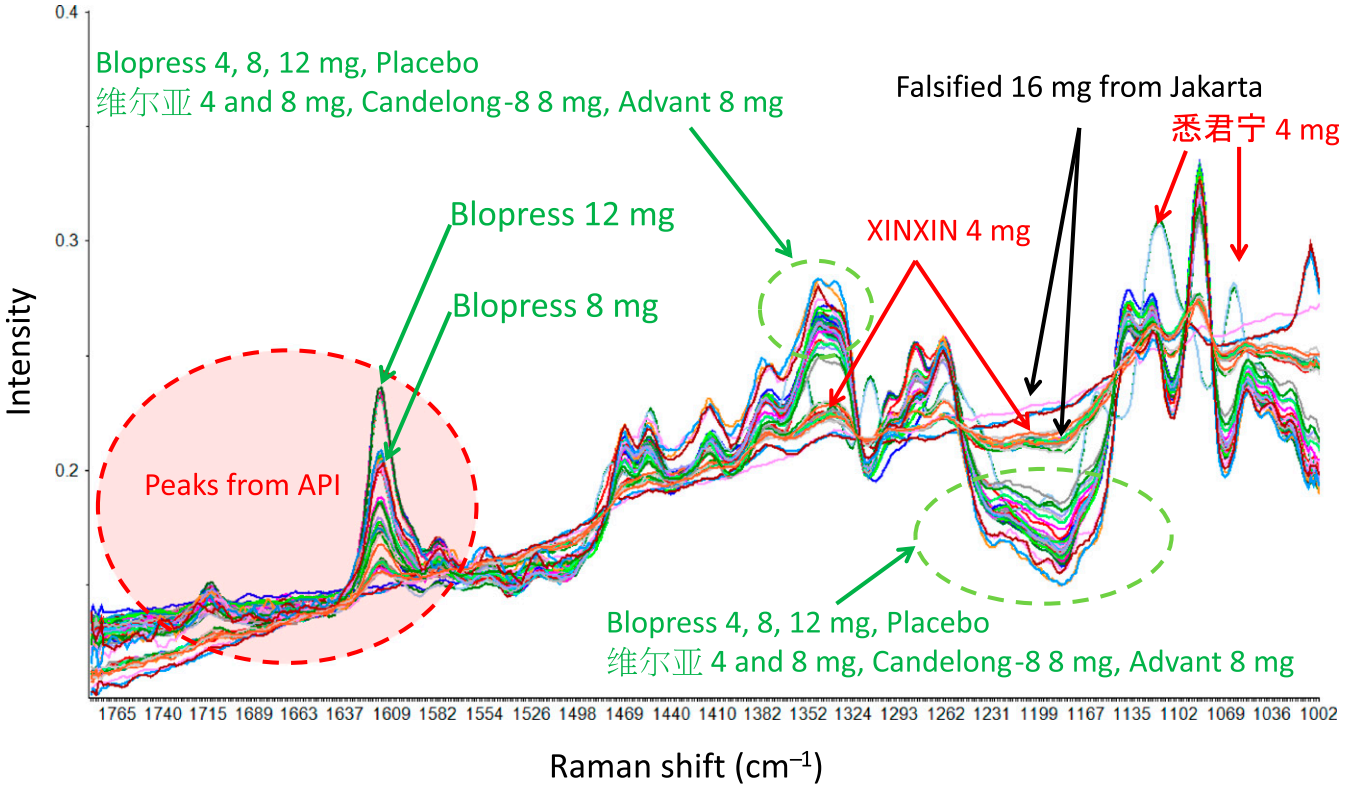

FIGURE 4. Raman spectra of candesartan cilexetil tablets and the falsified products (after multiplicative scattering correlation preprocessing of Raman spectra). This figure appears in color at www.ajtmh.org.

spectra of the falsified products and products stated as XINXIN showed a distinctive upward slop of the baseline toward high wavenumber. The API peak intensity in this region was reported to increase linearly with the increase in API content in the tablets,[34,50] and a similar result was also obtained in this study. These relationships of the quantitation between the API peak intensity and the assay of the API in tablet were also confirmed in not only the weight measurement of API versus the peak intensity of Raman spectra but also the relationship between the weight measurement of API versus the peak intensity of X-ray diffraction measurement.[50]

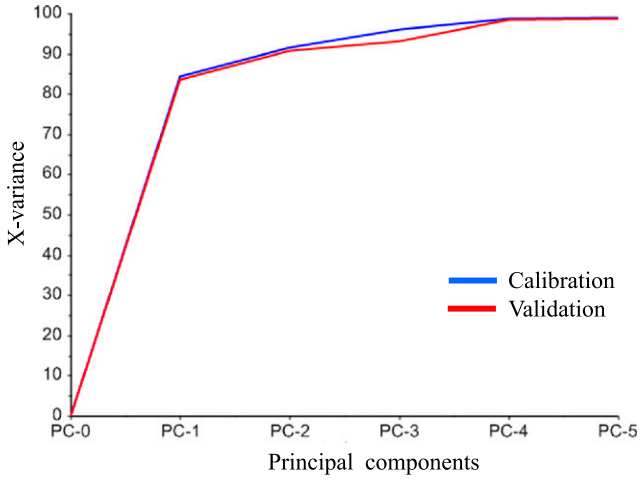

FIGURE 5. Comparison between the calibration model and validation result in principal component analysis model. This figure appears in color at www.ajtmh.org.

These Raman spectra were conducted preprocessing and subjected to PCA to investigate the similarity of chemical components among samples. Figure 4 shows the spectra after the preprocessing of SG method for smoothing and MSC method for baseline correction for the Raman spectra. The calibration result and the cross-validation result in the PCA model were compared as shown in Figure 5. The result suggested that the difference among the samples can be clarified by using the two principal components of PC1 and PC2, and the intensity change of Raman spectrum can be sufficiently expressed by PC1 and PC2. Therefore, the score plot was shown with the score of the PC1 and PC2 on the horizontal axis and the vertical axis and the vertical axis, respectively, for each tablet as shown in Figure 6. Data set of the Raman spectra in the range of 1780–1700 cm^{-1}, which includes peaks from the API and main excipient6s, showed the intuitive interpretation score plot in the PCA result. Tablets collected in Myanmar were distributed around authentic Blopress tablets in the score plot, suggesting that the similar excipients were used in both cases. On the other hand, the tablets collected in China showed a wide distribution on the score plot, suggesting that different excipients were used by different manufacturers. Notably, the tablets stated as XINXIN were placed very far from the other tablets and there was a high positive correlation in PC1, and the falsified products collected in Indonesia were located similarly in the plot. The falsified products included the API but clearly insufficient assay of the dose displayed on the package (16 mg), as judged from both the Raman spectra and the PC2 correlation compared with

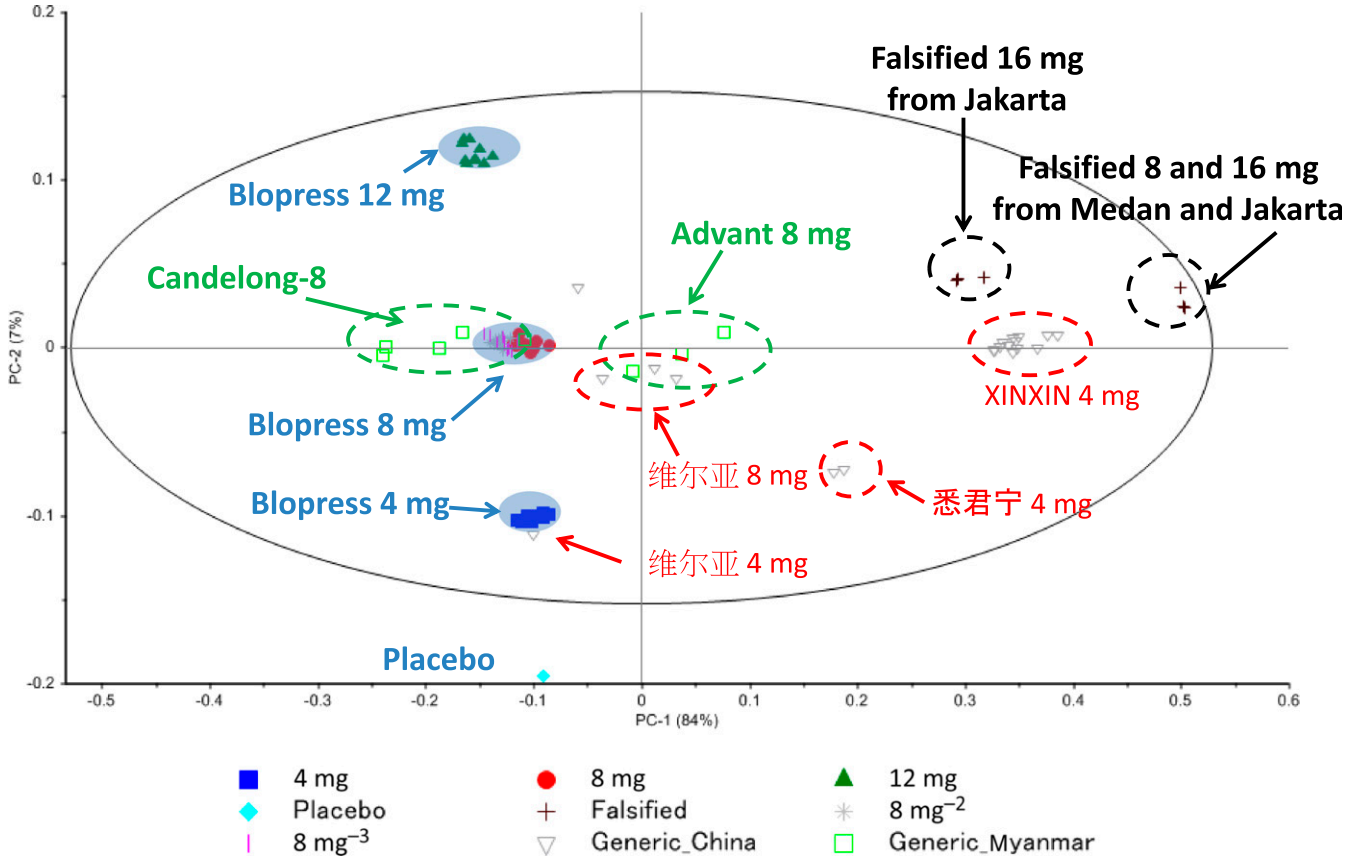

FIGURE 6. Principal component analysis score plot derived from the Raman spectra of candesartan cilexetil tablets, including the falsified tablets, collected in China, Indonesia, Japan, and Myanmar. This figure appears in color at www.ajtmh.org.

that of the authentic products. This result was in agreement with the result of the additional assay measurement (assay: about 60%) obtained using HPLC. In addition, both SFs contained almost the same amount of API, despite being labeled on the packages as having 8 mg and 16 mg, respectively, suggesting that these were falsified products with poor quality control.

Figure 7 shows the loading of each principal component (PC) in the calculated PCA model. The contribution rates were 84% of PC1, 7% of PC2, and 5% of PC3. PC2 was shown as a component that extracted the characteristics of the signal derived from API, whereas PC1 showed the characteristics of the excipients of the lactose and other excipients in the wave number region of 1200–1000 cm^{-1}. PC3 appeared to be mainly due to lactose factor.

DISCUSSION

Candesartan cilexetil tablets distributed in China, Indonesia, and Myanmar were made by various manufacturers and contained different kinds of excipients. Testing identified a number of samples with unacceptable API contents above or below the criteria limit of the Japanese pharmacopeia, and others with excessive dissolution delay. The failed samples that did not meet the criteria were all located far from the center in PCA score plot. Principal component analysis was also very effective in distinguishing different excipients, which appeared in different regions of the score plot. Principal component analysis result was able to explain all spectra clearly with two components, i.e., the medicinal ingredient and the excipient, including lactose. The PCA result decomposed spectrum reflected the elements of pure Raman spectrum on PC2 without interference by background of strong florescence substances. In this study, with an appropriate spectral preprocessing and PCA combination, even in market research using a large amount of Raman spectrum of various kinds of tablets, including some unknown excipients, the elements of the API and the kinds of the excipients are clearly extracted, and the similarity and correlation are clearly visualized.

A key feature of the present work was the use of the MSC method for Raman signal preprocessing. This method proved to be more effective than other commonly used methods, such as the second derivative and standard normal variate methods, for extracting the desired signals from the strong fluorescence background. It was found how to extract the chemical information itself from the spectra of the spectroscope, not the experimental devices and methods, is a significant powerful and effective solution for detecting SFs. These results suggest that the handheld Raman deice we used could be a useful tool to detect SFs in the field, despite its relatively low sensitivity and low resolution.

In conclusion, the combination of pharmacopeial quality control tests and PCA score plots calculated from Raman spectra proved to be a very effective methodology for detecting SFs. Application of this approach to candesartan cilexetil tablets collected in several Asian countries uncovered a number of examples of out-of-specification content and

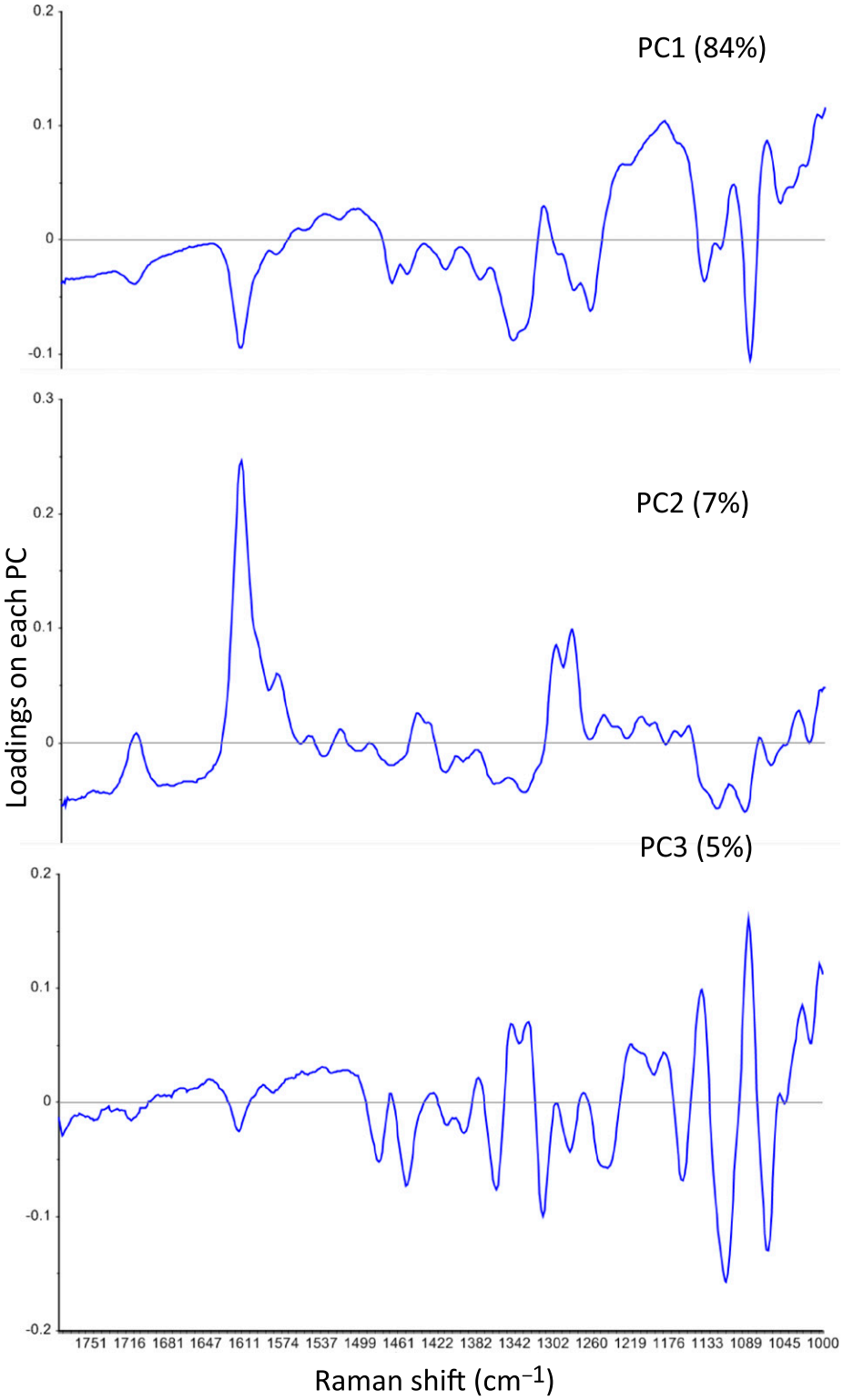

FIGURE 7. Loading on PC 1, PC 2, and PC 3 in the principal component analysis model calculated by using Raman spectra of candesartan cilexetil tablets. This figure appears in color at www.ajtmh.org.

inadequate dissolution. The handheld Raman device is expected to be useful in field surveys to detect SFs. Principal component analysis of that Raman data clarify the difference in chemical properties between good quality products and SFs that circulate in the Asian market.

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