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Rapid Screening of Anti-Infective Drug Products for Counterfeits Using Raman Spectral Library-Based Correlation Methods

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Abstract:

A new spectral library-based approach that is capable of screening a diverse set of finished drug products using only an active pharmaceutical ingredient spectral library is described in this paper. This approach obviates the need for a comprehensive drug product library, thereby streamlining the use of spectral library-based tests for anti-counterfeiting efforts, specifically to target finished drug products containing the wrong active ingredient or no active ingredient at all. Both laboratory-based and portable spectrometers are used in the study to demonstrate the usefulness and transferability of the spectral correlation method for field screening. The spectral correlation between the active pharmaceutical ingredient and finished drug product spectra is calculated using both full spectral analysis and targeted spectral regions analysis of six types of antimalarial, antibiotic and antiviral products. The spectral regions were determined using a moving window spectral correlation algorithm, and the use of specific spectral regions is shown to be crucial in screening finished drug products using only the active pharmaceutical ingredient spectrum. This comprehensive screening spectral correlation method is tested on seven different validation samples from different manufacturers as those used to develop the method as well as simulated counterfeits which were prepared to mimic falsified drugs containing no active ingredient. The spectral correlation method is successful in correctly identifying 100% authentic products and simulated counterfeit samples tested.

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Introduction:

The presence of counterfeit drug products in the pharmaceutical supply chain is a world-wide issue[1] that is especially prevalent in emerging countries. Counterfeit drugs have the potential to also infiltrate the supply chain of countries with established safeguards due to the ease in which prescription drugs may be purchased over the Internet.[2, 3] The broad class of anti-infective drugs comprising antibiotics, antiviral and antimalarial drugs has often been an attractive target[4-10] for counterfeits since these drugs are often used in emergency situations such as outbreaks or pandemics where the supply of bona fide drugs may be limited. Portable spectroscopic instruments have yielded promising results in detecting counterfeit or falsified drugs. Field-deployable spectroscopic methods using portable instruments have the potential to enhance public safety by dramatically increasing the number of products that undergo a physical test, typically requiring less than one minute.[11] In particular, Raman spectroscopy has proven to be successful in field applications involving portable units[12] for identification of samples and counterfeit detection in the field.[13, 14] Raman is capable of performing non-destructive screening through packaging and preserving suspect samples intact should further testing be necessary. Raman has been used with a wide range of chemometric methods[15-19] and allows for both qualitative and quantitative analysis. One of the most common approaches is the use of spectral correlation (SC) based library methods. Such SC methods are easy to implement since they typically do not rely on rigorous, product-specific method development and can be easily implemented without specialized software. SC methods are capable of performing qualitative verification or identification of a broad range of materials by comparing the sample under study to a reference spectrum contained in a spectral library.[20]

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Despite their ease of use, SC methods are limited by two main issues: 1) poor transferability of libraries between instruments and 2) lack of comprehensive libraries. The first issue stems primarily from physical differences in the optical components present in each spectrometer, which give rise to spectral differences that must be corrected. To address this issue, we have developed a practical three-step standardization algorithm to facilitate library transfer[21] across different instruments. The second issue is harder to solve, since "ideal" libraries would have *every* possible material represented in the library, which is clearly a difficult task. A comprehensive library of U.S. FDA approved finished drug products alone, for example, would require having ~100,000 unique entries![22] The finished drug product screening SC method presented in this paper focuses on using one, single representative active pharmaceutical ingredient (API) spectrum as a reference library spectrum for each type of drug, rather than attempting to include each individual formulation. Thus, the library can be used to screen any form of drug product (e.g., capsule, tablet, etc.) so long as the reference spectrum of the pure API found in the drug product is included in the library. In this work we focus only on drug products that contain one single API and are high API content drugs—that is the API composition is ~60% w/w of the dosage form mass. The scope of this paper is to screen anti-infective drugs which play an important role in controlling outbreaks such as pandemic flu and malaria, for example. These medicines play a vital role in public health and have proven to save lives when safe and effective medicines are available.

The purpose of this paper is to develop a SC method to screen finished drug products for the presence of counterfeits using only an API library. The types of counterfeit drugs targeted by this screening method are those that contain the wrong API[1] or no API at all. This technique is a qualitative screening technique that can be used to confirm the presence of the declared, or label-

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claimed API in a finished medicine. As a screening technique, the SC method presented here is meant to be a first-pass approach to identify suspicious samples that need further testing—which usually involves traditional laboratory testing to perform quantitative compendial testing such as assay, release and impurities.

The Raman spectrum of a finished drug product contains signatures of all the materials in the formulation including the inactive ingredients (excipients), coatings and dyes. By narrowing the scope of the spectral correlation test to only those regions where API peaks are present, the influence of the other materials in the formulation are minimized or eliminated altogether. Unique spectral regions were identified for each class of pharmaceutical product studied by adapting a recently-published moving window algorithm, which was successfully applied to a near infrared library to facilitate differentiation of crude oil samples.[23, 24] Here we utilize the moving window spectral correlation coefficient algorithm for determining optimal regions for a set of finished drug products based on comparison of the API and finished drug product Raman spectra. The use of variable selection algorithms, such as the moving windows correlation coefficient algorithm, to improve the sensitivity of chemometric methods is common and has been employed to enhance the performance of partial least squares models.[25] Numerous variable selection algorithms are available and have been used with a wide array of different chemometric techniques to enhance sensitivity and specificity.[25, 26] Regression, uninformative variable elimination, simulated annealing, and interval selection (including interval partial least squares, e.g.[27]) are some types of algorithm categories[26] that have been reported.

The spectral regions chosen to identify the products analyzed in this study contain predominantly the features present in the API spectrum, and therefore the SC methods are

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independent of the drug manufacturer, dosage form and dosage strength of the finished product. The SC method is validated using an independent data set containing authentic finished drug products and simulated counterfeits on both laboratory-based and portable instruments. The SC method is shown to be highly accurate, yielding appropriate "pass" results with no false positives for the independent validation samples studied.

Experimental Methods:

Spectral Acquisition and Sample Preparation. All spectra used in this study were treated with the previously published standardization protocol prior to comparison[21] and the API library has been detailed and evaluated elsewhere.[28] Method development and validation was performed by acquiring spectra of samples of authentic finished drug products from different manufacturers along with simulated counterfeit products. All drug products used in this study were purchased commercially and used without further preparation except for the simulated counterfeit samples which were prepared in house as described below. The full roster of calibration and validation samples is included in Table 1. The drugs in this study have relatively high API composition (~60% w/w) in the dosage form. Calibration and validation sample spectra were acquired in the 250-1900 cm^{-1} spectral region using a laboratory-based Kaiser Optical Systems Raman WorkStation. The spectrometer utilized 785 nm excitation, and the laser power measured at the sample was ~260 mW. A wide-beam (P^hAT) probe was used that interrogated samples with a spot size of 3 mm. The spectrum for each individual drug product used for model building was based on the average spectra of 12 different tablets/capsules. Performance of the SC method on portable instruments was studied using the spectra of validation samples acquired in the 350-1800 cm^{-1} spectral region on a B&W Tek MiniRam II portable Raman spectrometer with 785 nm

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excitation with ~300 mW laser power and ~3 mm spot size using a tablet holder accessory. Calibration samples were used to determine the API-specific spectral ranges for the different types of drugs studied. Validation samples included the same type of drugs as those in the calibration set but from different manufacturers. Five simulated counterfeit quinine sulfate capsules were prepared and also used for validation. The simulated counterfeit capsules were made using authentic capsules from manufacturer V filled with corn starch. The authentic capsule-form products were twisted open, keeping the capsule shells intact, and emptied. Corn starch from an in-house excipient library was poured into the capsules to at least one-third full and the capsules were reassembled, inverted several times, opened, and emptied. This corn starch rinse was performed three times for each capsule. Finally, the capsules were then filled with corn starch to similar weights (±0.005 g) as the authentic capsule.

Spectral Preprocessing. Raw spectra were treated with first derivative preprocessing (2nd order, 31-point Gram polynomial convolution filter).[20] Spectra were then truncated to an appropriate spectral range: either the optimum spectral region for each API (using the procedure described in the next section) or 350-1800 cm^{-1} for full spectral region analysis, which is the common region for all spectrometers used.

Spectra were compared by calculating the spectral correlation value, called SC value here. The SC value[20] is a measure of the similarity between the sample under study (Unknown) and reference (Library) spectra and is calculated according to Equation 1.

$$SC = \frac{(Library \cdot Unknown)^2}{(Library \cdot Library)(Unknown \cdot Unknown)} \quad (1)$$

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The SC is the square of the spectral covariance and SC values range between 1.000 (for perfect correlation) and 0 (for poor correlation). A typical pass/fail threshold is 0.95. Variability in the noise levels across spectra of the same sample causes SC values to always be less than 1 unless they are computed from identical samples. Smoothed first derivative preprocessing reduces the influence of differences in baseline on the SC value and enhances spectral features of interest.

API-Specific Regions. In SC method development, unique spectral regions were determined for each of the different types of finished drug products listed in Table 1 by applying the moving windows spectral correlation (MWSC) algorithm which was adapted from the previous moving window algorithm study.[23, 24] An example of the typical Raman spectra obtained for API and finished drug product is shown in Figure 1a for quinine sulfate, and the corresponding first derivative spectra are shown in Figure 1b. The algorithm iteratively calculates the SC value between the API and finished drug product first derivative spectra within a 151 point window, moving the window on a point-by-point basis across the entire spectral range of the Raman spectrum. The SC value calculated for a given window is assigned to the Raman shift location at the center of the window. This technique produces a spectrum of SC values and is useful in showing the spectral ranges where the correlation between the finished drug product and the API first derivative spectra are the strongest. These spectral ranges correspond to the regions in the finished drug product spectrum that may be used in a spectral correlation test to confirm whether the label-claimed API is present in the drug product.

An example of the SC plot generated from the algorithm is shown in Figure 1c for the quinine sulfate API and finished drug product pair. As can be readily noted from Figure 1c, there are two general regions where the SC values are above the traditional 0.95 threshold, 747-

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820 cm^{-1} and 1275-1458 cm^{-1}. Upon comparison with Figures 1a and 1b, it is apparent that these two regions correspond to areas where there are meaningful peaks in the raw and first derivative spectra. Such comparison between the raw and first derivative spectra is crucial in picking the correct region(s) and is the first of the four criteria that are used to determine the most reliable regions for each different type of drug product. As a second criterion, the areas identified by the algorithm must occur over a region where there are noticeable Raman bands with adequate signal to noise ratio (greater than > 1.2) in the raw spectrum. Thirdly, we required regions to be at least 20 cm^{-1} wide to decrease the possibility that a random spectral artifact in either the API or finished drug product would give rise to an anomalous spectral range. Finally, the algorithm was carried out on at least three different manufacturers when trying to find the optimum regions for a type of drug product. This last requirement aids in assuring that variability between different manufacturers is incorporated into the model development. Once the MWSC plot was determined for each of the finished drug products in the calibration set for each drug type, the common spectral regions were identified and then evaluated using the above criteria. For SC method evaluation, single SC values were calculated for full spectral range and optimized spectral regions, using Equation 1 to compare the Library and Unknown spectra.

Results and Discussion:

The optimum spectral regions for each type of drug included in this study are shown in Figure 2a-f along with the API spectrum and a representative drug product. The regions are also listed in Table 2. During SC method evaluation, single SC values were calculated by comparing spectra of APIs to the finished drug products containing the same API using both the full spectral range and the optimum spectral regions listed in Table 2. The same drug products were used for

each analysis, with results shown in Figure 3a and 3b, respectively. The number of calibration samples used in SC method development are listed in parentheses ( ) and also listed in Table 1. While the average value for each of the different types of drugs are generally above 0.95 for both full spectral range and optimized spectral region, the range of values is noticeably broader when using the full spectral range. Moreover, several SC ranges fall below the desired 0.95 threshold. This is likely due to the SC values for drug products from different manufacturers being influenced by the unique characteristics of each drug product including different excipients, dyes and coatings. These attributes introduce new spectral features across the full spectral range, which result in varying SC values for finished drug product spectra compared to library API, which is free from any excipients, coatings, etc. The averages and ranges for the SC values are more similar to one another for the six different types of products studied using the optimized spectral regions. The average SC values are higher than those for full spectral range. More significantly, the ranges for all six drug product sets are now above the desired 0.95 threshold.

A subset of the calibration set was further analyzed to determine whether the use of spectral regions affects the ability of the SC method to distinguish between structurally similar drugs. Anti-malarial drugs containing either chloroquine, hydroxychloroquine or quinine sulfate were chosen to examine the performance of closely related drugs by optimized spectral ranges versus full spectral regions since it is possible that features that distinguish closely related drugs may not be included when using narrower regions. Figure 4 shows a spectral correlation diagram for these drugs compared to one another. Spectral correlation diagrams are useful in identifying specific entries in the library where different drug products may pass screening for one another (i.e., yielding false passes) when using only API library as the reference spectra. The three different APIs (vertical elements) are compared to the three different types of finished

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drug products from different manufacturers (horizontal elements). A color-coded scheme is used to indicate SC values with green elements corresponding to SC values from 0.95 to 1 (Pass). Two other colors are used to indicate varying levels of correlation below 0.95. Both full spectrum results and optimized spectral region results reveal no false positives (i.e., no finished drug products with correlation values above 0.95 for the wrong API). Thus, the use of the API spectrum to predict the identity of finished drug products is an approach that works well. Furthermore, the optimized spectral regions do not lessen the specificity of the SC method for distinguishing between drug products from the same family. There are three yellow boxes, one for chloroquine and two for hydroxychloroquine drugs, which correctly indicate spectral similarity between the drug product and associated API, but the SC values are below the 0.95 threshold. These three authentic finished drug products would have failed the test using the 0.95 threshold on the full spectral range comparison. All products pass when using the optimized spectral region for each of the different types of drugs. This result shows that the optimizied API-specific spectral region approach is able to more effectively focus on the API signature and ignore areas of the spectra where different formulations of the same drug may cause even authentic products to fail.

The SC method developed is aimed at providing reliable results for any finished drug products claiming to contain one of the APIs in the reference library. To this end, we attempted to validate the performance of the optimized spectral region SC methods for finished drug products not included in the calibration set. A list of the validation samples for each type of drug product is included in Table 1. The six sample validation set was run on both laboratory-based and portable instruments since these SC methods are designed to be used in rapid manner in the field. The finished drug spectrum is compared to the entire API library by calculating SC values;

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the SC method then generates a list of reference matches from the API library that are ranked by SC value for each drug product analysis. The resulting top match for each drug product is shown in Figure 5, along with the second-ranked match. There is remarkable agreement between the values for the laboratory-based and portable instruments, indicating that these SC methods are transferrable across different instruments and platforms. This attribute is important since transferability of Raman methods across instruments is not usually straight-forward. SC values for all samples were above the 0.95 threshold, and the identity of the top match was always the claimed API. The previously noted structural relationships between the APIs of chloroquine phosphate, hydroxychloroquine sulfate and quinine sulfate were reflected in the SC values for the sample drug products containing those APIs. The second match was always one of the other two related APIs. These SC values were relatively high among the second matches for the different drug product groups, but still below the 0.95 threshold, resulting in no false passes for any sample drug product in this study.

To further demonstrate the utility of the universal drug product screening SC method for detection of counterfeit drug products by portable instruments, authentic and simulated counterfeit quinine sulfate samples were analyzed by the portable Raman instrument. The authentic and simulated counterfeit samples appear to be similar by visual and physical inspection, as shown in Figure 6a. Comparison of the spectral library reference spectrum (shown in Figure 6b) and the authentic capsule spectrum (shown in Figure 6c) reveals that the optimized peaks for the API quinine sulfate are clearly present in the authentic capsule spectrum, particularly the peak at 1365 cm^{-1}. That peak is absent in the spectrum of one of the counterfeit capsules (comprised of corn starch), shown in Figure 6d. Using optimized API-specific region analysis, a single SC value for each capsule spectrum with the quinine sulfate API spectrum was

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calculated. The authentic sample was found to have an SC value of 0.977, and the five counterfeits had an average SC value of 0.088 ± 0.018 . Thus the counterfeit samples correctly fail the screening test using the portable spectrometer.

Conclusions:

The optimized spectral regions library SC method is a unique application of identification-based SC methods that is capable of performing identification tests on finished products both in the laboratory and, more importantly, on field instrumentation. This approach was shown to be amenable to anti-counterfeit rapid screening of finished drug products in the broad class of anti-infectives, using only the API spectrum as the reference library spectrum. This qualitative SC method enables stream-lined use and reduced maintenance of a spectral library for initial screening of drug products to confirm the presence of the declared or labeled API. This method was shown to be 100% correct in confirming the labeled API and was able to correctly predict all the simulated counterfeit as failing samples since they did not contain any API. The accuracy of the optimized spectral regions library SC method shows that this technique can be a powerful qualitative tool for screening for suspicious drugs.

The use of spectral regions, tailored for individual APIs, improves spectral correlation between the sample drug product and its API spectrum. Drug product sample spectra are dominated by the strong spectral features of APIs that lead to high specificity of this SC method, as shown in method validation. The optimized spectral regions library SC method is dependent on the quality of drug product spectra and the presence of API peaks in those spectra. The drug products studied here included capsules, coated tablets, and non-coated tablets with high API content ~60% w/w of the dosage form mass. They all were analyzed successfully with this SC

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method. For extension of this SC method to drug products containing other APIs, initial testing of the SC method on at least three drug products is recommended to determine spectral quality and optimize the region for SC analysis. The promising results of the quinine sulfate capsules shows that Raman SC method developed can screen for counterfeit samples even when the fake capsules appear to be visually identical in appearance, size and shape to the authentic version. These findings have broad implications in the development of rapid, high throughput spectroscopic screening methods not only for counterfeit anti-infective drugs but for other medicines as well. Rapid screening of finished products has the potential to enhance public health by increasing the number of products that undergo physical testing before reaching consumers and ensuring the availability of quality medicines. Further testing of the SC method is necessary to assess the usefulness of the SC method for products with low levels of API such as those used in high potency formulations where the API comprises a much lower percentage of the dosage form mass.

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Table 1. Method calibration and validation set of drug products, listed by API, designation, and then dosage.

Manufacturer	Drug Product	Dosage (mg)	Dosage Form	Designation
A	Chloroquine phosphate	500	Tablet	Calibration
B	Chloroquine phosphate	500	Tablet	Calibration
C	Chloroquine phosphate	500	Tablet	Calibration
D	Chloroquine phosphate	500	Tablet	Validation
E	Ciprofloxacin HCl	100	Tablet	Calibration
D	Ciprofloxacin HCl	250	Tablet	Calibration
F	Ciprofloxacin HCl	250	Tablet	Calibration
G	Ciprofloxacin HCl	250	Tablet	Calibration
D	Ciprofloxacin HCl	500	Tablet	Calibration
G	Ciprofloxacin HCl	500	Tablet	Calibration
H	Ciprofloxacin HCl	500	Tablet	Calibration
D	Ciprofloxacin HCl	750	Tablet	Calibration
I	Ciprofloxacin HCl	750	Tablet	Calibration
J	Ciprofloxacin HCl	750	Tablet	Calibration
E	Ciprofloxacin HCl[a]	250	Tablet	Validation
I	Ciprofloxacin HCl[b]	250	Tablet	Validation
C	Hydroxychloroquine sulfate	200	Tablet	Calibration
D	Hydroxychloroquine sulfate	200	Tablet	Calibration
G	Hydroxychloroquine sulfate	200	Tablet	Calibration
K	Hydroxychloroquine sulfate	200	Tablet	Calibration
L	Hydroxychloroquine sulfate	200	Tablet	Calibration
M	Hydroxychloroquine sulfate	200	Tablet	Validation
N	Levofloxacin	250	Tablet	Calibration
O	Levofloxacin	250	Tablet	Calibration
P	Levofloxacin	500	Tablet	Calibration
Q	Levofloxacin	500	Tablet	Calibration
R	Levofloxacin	500	Tablet	Calibration
S	Levofloxacin	500	Tablet	Validation
L	Metronidazole	500	Tablet	Calibration
L	Metronidazole	500	Tablet	Calibration
R	Metronidazole	500	Tablet	Calibration
T	Metronidazole	500	Tablet	Calibration
L	Metronidazole	250	Tablet	Validation
P	Quinine Sulfate	324	Capsule	Calibration
Q	Quinine Sulfate	324	Capsule	Calibration
U	Quinine Sulfate	324	Capsule	Calibration
V	Quinine Sulfate	324	Capsule	Validation
V	Quinine Sulfate[c]	0	Capsule	Validation

a. Run only on laboratory instrument.

b. Run only on portable instrument.

c. Five simulated counterfeit samples using the capsule shells from manufacturer V.

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Table 2. Optimized spectral ranges for each API and associated drug product group.

API	Region 1	Region 2	Region 3
Chloroquine phosphate	829-996 cm^{-1}	1015-1199 cm^{-1}	1278-1701 cm^{-1}
Ciprofloxacin HCl	1297-1725 cm^{-1}		
Hydroxychloroquine sulfate	747-815 cm^{-1}	1050-1134 cm^{-1}	1285-1688 cm^{-1}
Levofloxacin	1473-1705 cm^{-1}		
Metronidazole	559-1637 cm^{-1}		
Quinine sulfate	747-820 cm^{-1}	1275-1458 cm^{-1}	

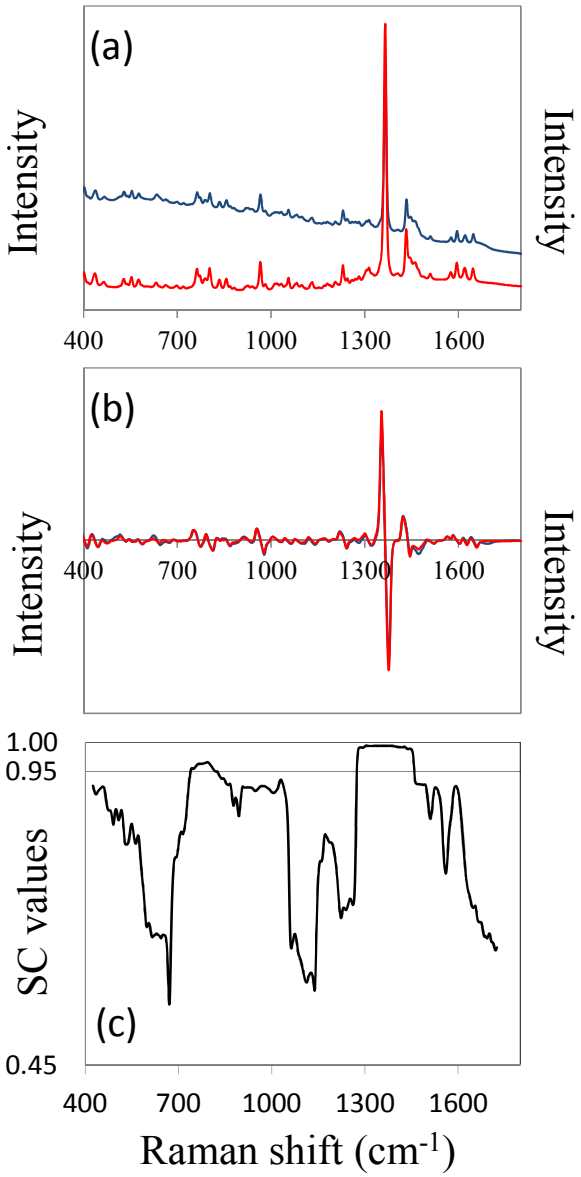

Figure 1. Moving Window Spectral Correlation (MWSC) method applied to quinine sulfate API and representative drug product (manufacturer Q) spectra. (a) Raw spectra, (b) first derivative spectra and (c) plot of SC values using MWSC method

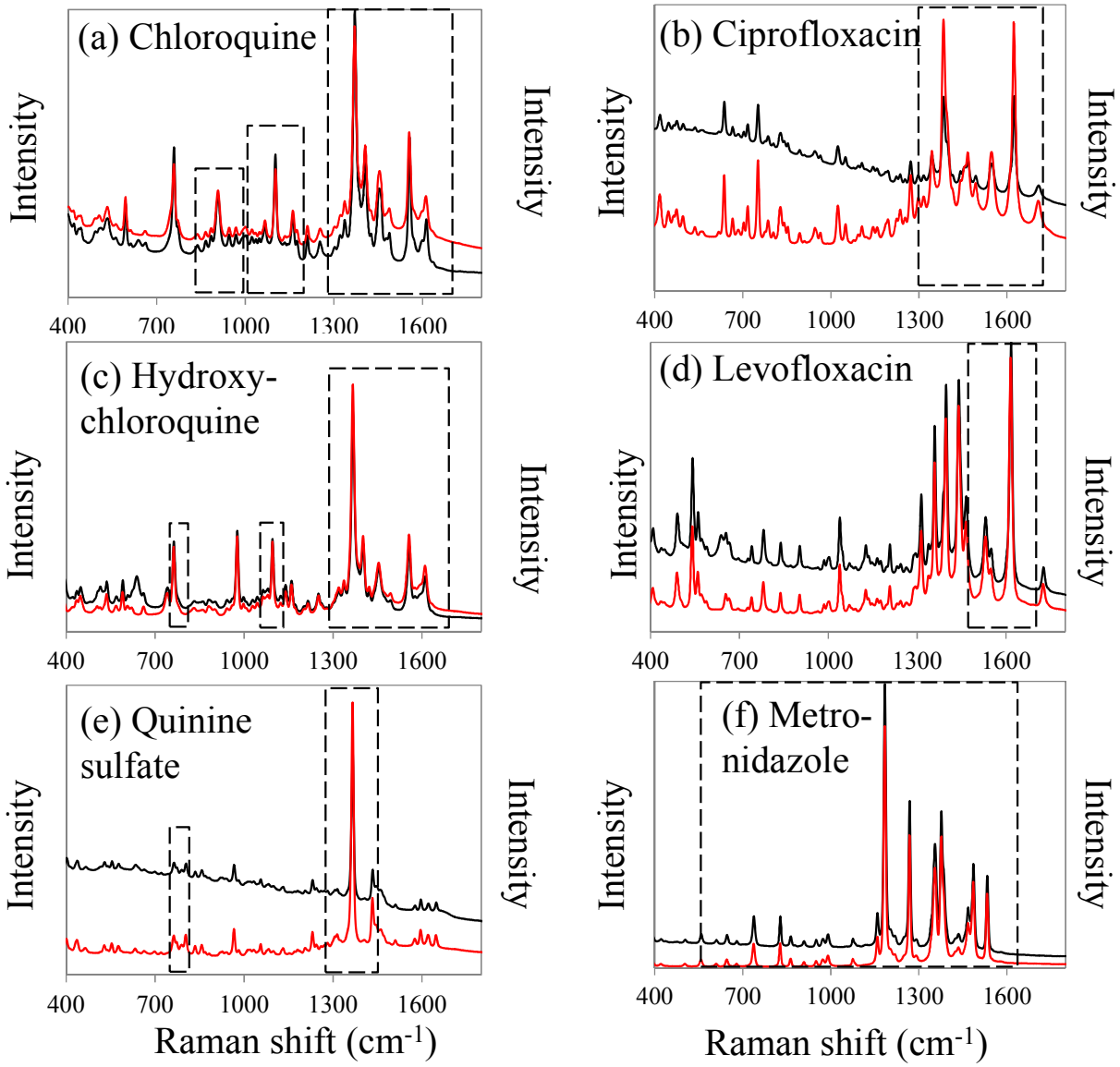

Figure 2. Overlay of Raman spectra for each API (red) with a representative finished drug product from calibration set (black). The API-specific regions are boxed.

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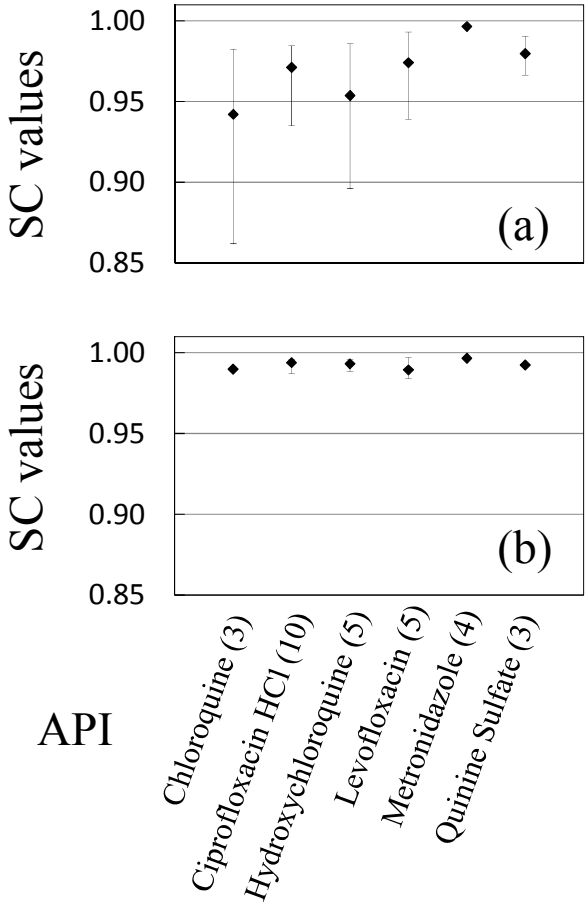

Figure 3. Effect of using (a) full spectral range versus (b) optimized API-specific region on single SC values for each drug product-API comparison. SC values were calculated for drug product spectra in the calibration with API library spectra, and grouped by API in the figure. The bars span the range of SC values. The numbers in parenthesis ( ) are the number of manufacturers in the calibration for drugs containing that specific API.

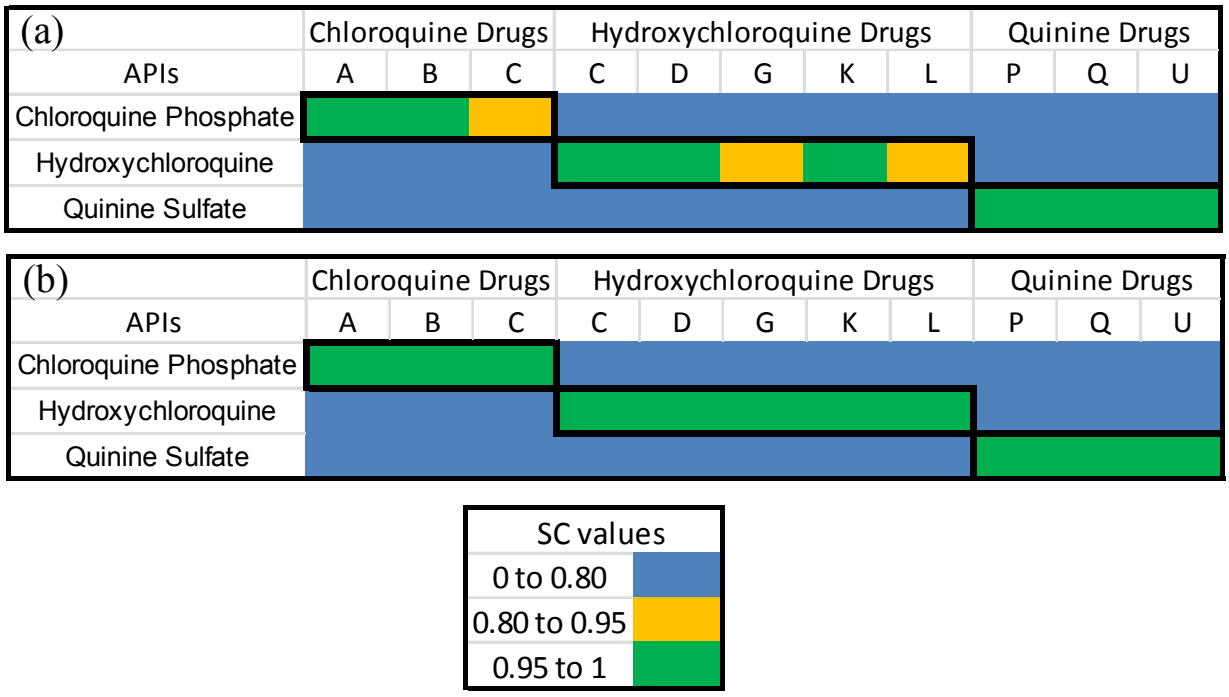

Figure 4. Spectral correlation diagrams from (a) full spectral analysis and (b) use of API-specific regions. Finished drug products are listed by API and manufacturer according to roster in Table 1.

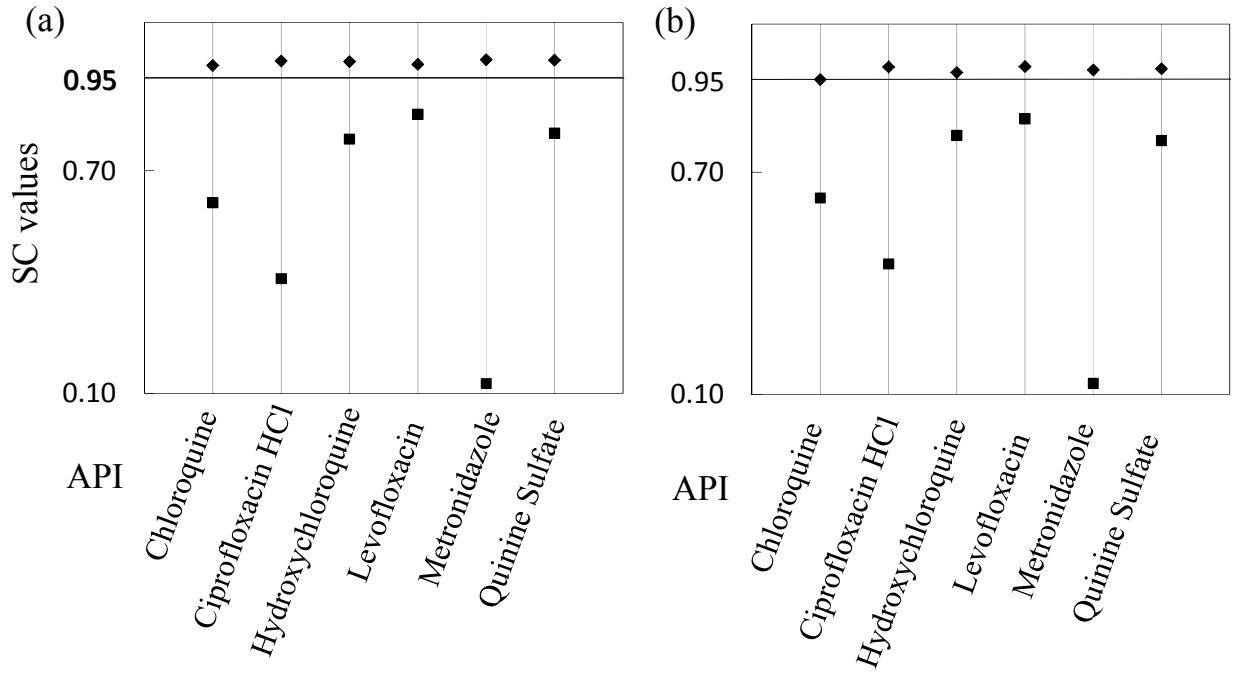

Figure 5. Plot of SC values for validation testing on (a) laboratory and (b) portable Raman instruments. Single SC values for each drug product-API comparison were calculated using API-specific regions given in Table 2. The diamond-shaped data points are the first match API spectrum; the square-shaped data points are the second match API spectrum. The first-ranked results matched the known identity of the drug product for all six types of drugs.

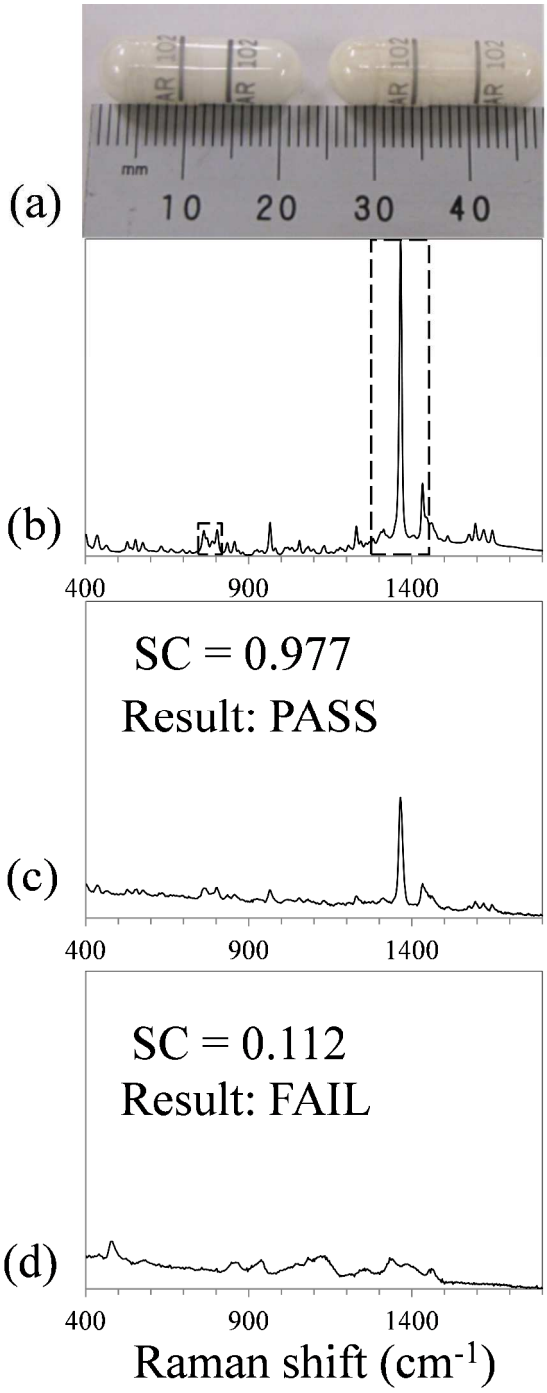

Figure 6. Visual and spectroscopic comparisons of authentic and simulated counterfeit capsules of quinine sulfate. (a) Authentic capsule (left) and simulated counterfeit capsule (right), (b) Raman spectrum of quinine sulfate API with spectral regions boxed, (c) Raman spectrum of authentic capsule and (d) Raman spectrum of simulated counterfeit capsule.

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