2018

Illicit and Counterfeit Drug Analysis by Morphologically Directed Raman Spectroscopy

Andrew Koutrakos
University of New Haven, AKoutrakos@newhaven.edu

Pauline E. Leary
Smiths Detection, Inc.

Brooke Weinger Kammrath
University of New Haven, bkammrath@newhaven.edu

Publisher Citation

Koutrakos, A. C., Leary, P. E., Kammrath, B. W. (2018). Illicit and Counterfeit Drug Analysis by Morphologically Directed Raman Spectroscopy. In Rabi Ann Musah, Ph.D. (Ed.), Methods in Molecular Biology: Analysis of Drugs of Abuse, pp. 13-27. Springer. ISBN: 978-1-4939-8579-1

Comments

Purchase the book or chapter at the Springer website.
Find the book in a nearby library.
This is a post-peer review, pre-copyedit version of a chapter published in Methods in Molecular Biology: Analysis of Drugs of Abuse. The final authenticated version is available online at: http://dx.doi.org/10.1007/978-1-4939-8579-1_2

Illicit and Counterfeit Drug Analysis by Morphologically Directed Raman Spectroscopy

Running Head:

Drug Analysis by MDRS

Authors:

Andrew C. Koutrakos, MS, Pauline E. Leary, Ph.D., Brooke W. Kammrath, Ph.D.

Abstract:

Morphologically directed Raman spectroscopy (MDRS) is a novel tool for the forensic analysis of illicit and counterfeit drug samples. MDRS combines Raman microspectroscopy with automated particle imaging so that physical and chemical information about the components of a mixture sample can be obtained. Results of automated particle imaging are used to determine samples for Raman analysis. The use of MDRS for these types of samples can be employed for both forensic investigations and adjudications of cases. The method provides insight about the physical and chemical composition of the sample, as well as about manufacturing and sample history. Here, MDRS was used in four different illicit and counterfeit drug analyses: (1) examination of a multi-component drug mixture where the results could be used for comparative source attribution, (2) the detection of low (or trace) concentration particles in a drug sample, (3) the analysis of synthetic cathinone samples (i.e., bath salts), and (4) a study of counterfeit pharmaceutical products.

Key Words:

Morphologically directed Raman spectroscopy, illicit drug analysis, counterfeit pharmaceuticals, Raman spectroscopy, automated particle imaging

1. Introduction:

Morphologically directed Raman spectroscopy (MDRS) combines the power of automated particle imaging with Raman microspectroscopy into a single platform. Particle imaging is performed to determine particle size and shape distribution of components in a blended sample. These are important physical properties of particulate samples and may have a direct influence on a sample's performance. Size and surface area of a particle can be related in a significant way to the physical, chemical and pharmacologic properties of a drug. Clinically, the particle size of a drug can affect its release from dosage forms that are administered orally, parentally, rectally and topically (1). Dissolution rate (2, 3), stability (3), flowability (4), viscosity, packing density and porosity (1) may all be dependent upon particle size of drugs and drug products.

Particle size and distribution are routinely measured across a wide range of industries because they are important, and sometimes critical, to the manufacture and performance of substances and products. This is especially true within the pharmaceutical industry. In spite of this importance, they are not widely used as methods for classification, identification or individualization in the forensic sciences. Raman methods are useful for determining molecular and physical chemistry because they are fast, reliable, non-destructive and non-contact methods. They are used in the pharmaceutical industry for a number of different purposes including identification of raw materials, quantitative analysis of chemical

composition in product formulations, and polymorphism screening and identification (5). Raman methods are also used in the forensic sciences for the analysis of many types of physical evidence including drugs, explosives and paints (6).

Independently, both particle imaging and Raman microspectroscopy are valuable methods. Even when combined into a single platform, analysis based upon each method's independent evaluation may be useful. However, the power of a combined platform is greater than the sum of the individual methods. Together, the data from these two methods may provide insight about the sample including its manufacturing method, history and quality. This type of information may be invaluable during analysis of evidence in forensic casework.

When performing MDRS, the sample's morphological data is collected using a light microscope with an automated stage. This allows for the sorting of particles based on various physical parameters (7)**.** Once this particle data is collected, these parameters are then used to automatically select particles for chemical analysis using Raman microscpectroscopy. The ability to perform particle selection for chemical analysis using physical parameters removes subjectivity in the measurement. In addition, the automation of the stage and of the particle selection removes the need to expose the analyst to the sample for the prolonged periods of time that would be required if manual measurements were performed (8)**.**

MDRS is an excellent tool for the analysis of illicit and counterfeit substances, not only because it provides physical and chemical information about the sample, but also because it can be used to classify, identify and even individualize a sample. Raman spectroscopy can be used for illicit drug analysis both in the laboratory and in the field by using portable Raman spectrometers (9)**.** However, traditional Raman methods employ bulk analysis, which risks missing particles in low concentrations of a mixture sample (10). Particle-specific chemical analysis mitigates this risk, which is important because

these particles may provide information about a sample that can be used to establish provenance, enabling the effective tracing of drug distribution routes and networks (11).

The internet, in many instances, has made the procurement of illicit substances easier than it was in the past. The abundance of synthetic cannabinoids and cathinones is a direct result of the inability to control online sales of drugs (12). These products may be marketed as wholesome products that offer legal highs, but are frequently far more insidious. In many instances, such as with bath salts or plant foods that are marketed like this, the product should not be consumed. When it is, it may cause sickness or even death (13). These synthetic products tend to mimic the effects of a stimulant rather than the hallucinogenic/depressive qualities of the active ingredient in marijuana, Δ9-tetrahydrocannbinol, the substance they are designed to emulate (14). They stimulate the CB1 and CB2 receptors of the brain like a typical cannabinoid, but unlike Δ9-tetrahydrocannbinol, they are total receptor agonists. With repeated use, they overload and eventually damage the receptor, resulting in delirium, brain damage and sometimes death (15).

Aside from the medical risks, these drugs are also a challenge to the criminal justice system for legal reasons. When one of these substances becomes illegal, synthetic chemists need only to make a slight modification to the chemical structure of the illicit compound to allow for the circumvention of legal prosecution. Independently, particle imaging is not capable of characterizing these small molecular changes to the drug. However, the addition of Raman microspectroscopy to particle imaging makes it possible to not only achieve this task, but also to uncover manufacturing and other information about the sample. This type of analysis is possible using MDRS even when only a small percentage of the mixture sample contains the illicit substance (16). This makes rapid identification of an unknown mixture very important, as these blends are sold as powders with distinct particle sizes, distributions and chemical structures. Characterization using MDRS may be very beneficial in these situations.

There is growing concern regarding the proliferation of counterfeit pharmaceuticals on the global market. Frequently acquired through online pharmacies in the United States, counterfeit drugs provide a number of medical and legal challenges and pose a risk to both the consumer and to the intellectual property (IP) owner (17). Risks to the consumer are usually health related, as there is no quality control in the counterfeit-drug trade. Risks to the IP owner are usually considered to be financial, but may also jeopardize the future development of pharmaceuticals (17)**.** MDRS proves to be a useful tool in the analysis of these spurious drugs, as it provides both the chemical and particle data (18). Pharmaceutical production is a tightly controlled business, where details down to the particle size are carefully managed. This is not true with counterfeits, and the lack of quality control in these is a boon for the analyst, as these differences could be used to trace back to a specific manufacturer.

To demonstrate the use of MDRS in illicit and counterfeit drug analyses, samples of multicomponent mixtures, drug samples containing trace-level concentration components, commercially available bath salts and counterfeit pharmaceuticals purchased from online pharmacies were analyzed.

2. Materials:

2.1 Determination of multicomponent drug mixtures

1. Samples: suspected illicit drug powder sample. As an example analysis, a mixture of 0.1 grams each of powdered cocaine, phenobarbitol, pentabarbitol, amphetamine and D-methamphetamine (Sigma Aldrich) were weighed and thoroughly mixed.
2. Analytical equipment and supplies: Malvern Morphologi G3-ID Particle Analysis System with Sample Dispersal Unit, Quartz plate, Isopropanol (Sigma Aldrich) for cleaning the quartz plate, and a 7 mm^3 sample scoop.

2.2 Detection of low concentration incipient particles in drug samples

1. Samples: suspected illicit drug powder sample. As an example analysis, a mixture of dextromethorphan hydrobromide (Sigma Aldrich) and baking soda (sodium bicarbonate) were combined in a 999:1 weight ratio.
2. Analytical equipment and supplies: same as those in section 2.1.

2.3 Analysis of commercial bath salts (i.e., synthetic cathinones)

1. Samples: suspected synthetic cathinone samples. As an example analysis, two commercially available synthetic cathinones, “Arctic Rush” and “Fast Forward”, marketed as “bath salts” were analyzed.
2. Analytical equipment and supplies: same as those in section 2.1.

2.4 Analysis of counterfeit pharmaceuticals

1. Samples: counterfeit pharmaceutical tablets. As an example analysis, three samples of Fildena, a generic male enhancement drug, was purchased from online pharmacies originating in Singapore (2 samples) and India (1 sample) and delivered to the United States were analyzed.
2. Analytical equipment and supplies: same as those in section 2.1, with the addition of a scalpel, mortar and pestle

3. Methods:

3.1 Determination of multicomponent drug mixtures

3.1.1. Analytical conditions

- 1. Disperse sample onto a quartz plate using a 4-bar dispersion pressure.

  2. Perform image analysis with the Morphologi G3-ID Particle Analysis System's optic system (a Nikon CFI 60), using a 10-times microscope objective. Capture greater than 100,000 particles per sample (see notes 1 - 3).

  3. The targeting criteria for chemical analysis is a circular equivalent diameter greater than 7.0 µm and a solidity greater than 0.75.

  4. Perform Raman analysis with the Morphologi G3-ID Particle Analysis System's Raman microspectrometer (a Kaiser RamanRxn1), which is equipped with a 785 nm semiconductor laser and a 50-times microscope objective. The Raman analysis parameters are listed in Table 1 (see note 4).

3.1.2. Procedure

1. Obtain suspected illicit drug powder sample.

2. Use the 7-mm^3 sample scoop to transfer sample to the sample dispersion unit (SDU).

3. Ensure the fittings and top of the SDU are secure.

4. Disperse sample onto quartz plate and analyze according to the conditions detailed in section 3.1.1. (see notes 5 - 8).

5. Each Raman spectrum should be compared to either an internally made Raman spectral library or a commercially available electronic Raman spectral library. These Raman spectral libraries can be added to the Morphologi software for ease of use. If no Raman spectral library is available, point spectra should be collected from analytical standards and stored using the library function.

6. Generate particle size distributions and other morphological data using the Morphologi software. The smoothing function should be increased to approximately 50 to provide a more even view of the distribution.

3.1.3. Data Analysis

1. Using the collected Raman spectra and particle information, obtain the number of components and their chemical identities
2. Data analysis can include a calculation of the particle count percentage and percentage volume for each of the drugs, as shown in Table 2. Although this information can be used for comparison between samples, it should not be used for quantitation because these values do not equate with weight percent.
3. Analysis of the particle size distributions, as shown in Figure 1, and the particle morphologies, as shown in Figure 2, of the components of a mixture can be used for comparison between samples for common source attribution.

3.2 Detection of low concentration incipient particles in drug samples

1. Analytical conditions are the same as those in section 3.1.1.

2. Procedure: Obtain suspected illicit drug powder sample, and follow steps 2-6 as detailed in section 3.1.2.

3. Data Analysis: The same type of data analysis can be performed as detailed in section 3.1.3, with sample results shown in Figure 3.

3.3 Analysis of commercial bath salts (i.e., synthetic cathinones)

1. Analytical conditions are the same as those in section 3.1.1.

2. Procedure: Use the 7 mm^3 sample to transfer sample to the SDU directly from the container, and follow steps 2-6 as detailed in section 3.1.2.

3. Data Analysis: The same type of data analysis can be performed as detailed in section 3.1.3, with sample results shown in Figures 4 and 5.

3.4 Analysis of counterfeit pharmaceuticals

1. Analytical conditions are the same as those in section 3.1.1, except a 2.5-times microscope objective is used for the image analysis instead of a 10-times objective.

2. Procedure: carefully incise the pill wrapping using a scalpel on each of the tablets, completely remove the wrapping, and crush pills gently in a mortar and pestle, do not pulverize them. Follow steps 2-6 as detailed in section 3.1.2.

3. Data Analysis: The same type of data analysis can be performed as detailed in section 3.1.3, except because these samples were in tablet form, they were gently crushed in a mortar and pestle before analysis. Sample results are shown in Figures 6 and 7.

4. Notes:

1. To capture the best information about the particle morphologies for image analysis, the microscope should be aligned to provide even illumination with no glare and minimal stray light.

2. The magnification used for MDRS analysis depends on the size of the particles, with larger magnifications required for smaller particles. The Malvern G3-ID instrument is capable of analyzing samples with a large range of particle sizes, ranging from less than 1 micron to greater than a millimeter, depending on the microscope objective. The morphological imaging can be done using any

magnification objective, with a typical system having the following five objectives (with their nominal particle size ranges): 2.5-times (13 µm – 1000 µm), 5-times (6.5 µm – 420 µm), 10-times (3.5 µm – 210 µm) and 20-times (1.75 µm – 100 µm), and 50-times (0.5 µm – 40 µm) magnifications. Multiple imaging maps can be made for a single sample using different objectives in order to acquire morphological information for samples with a wide range of particle sizes. The position (x-, y-, and z-coordinates) of each particle is then recorded for subsequent Raman analysis, which uses the 50-times objective.

3. Ensure the laser guard veil is in place before attempting analysis. If not, stray light will interfere with the analysis. The chemical analysis portion will fail even if the automated image analysis completes.

4. The spot size for Raman analysis is fixed at 3um. However, Raman spectra can be obtained from smaller sized particles, especially those that are strong Raman scatterers.

5. If the sample is difficult to disperse using compressed air, it is possible to dissolve the sample in isopropanol, sonicate into suspension and place a few drops of the sample onto the analysis plate. After the isopropanol evaporates, analysis can be carried out as normal. This process was not needed for any illicit or counterfeit sample that the authors have encountered, and all samples have been able to be dispersed by compressed air. However, this method has found use with other analyses, thus is worth noting. If performed, it is important to note that dissolving and recrystallizing the sample in isopropanol or any other solution may alter particle size, shape and crystal structure of the recrystallized particles and, therefore, should be considered during data interpretation if this step is performed.

6. If there is significant particle aggregation, heating the sample for 20 minutes at 60°C followed by normal dispersal is typically enough to break apart these aggregates. Be sure the temperature is moderate so that no change in physical or chemical structure of the individual particles occurs.

7. Ensure all fittings on the SDU are tight and there are no leaks. If there are leaks, the result will be an incomplete or failed dispersion.

8. After cleaning the SDU or the quartz plate with isopropanol, wait at least ten minutes to ensure the instrument is completely dry to prevent clogs in the SDU or false positives from a contaminated plate. Ensure the inside of the SDU unit is clean as well using isopropanol and a lint-free cloth.

References

1. Martin A, Swarbrick J, Cammarata A (1983) Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 3rd ed. Lea & Febiger, Philadephia, PA
2. Iranloye TA, Parrott EL (1978) Effects of Compression Force, Particle Size, and Lubricants on Dissolution Rate. J Pharm Sci 67(4):535-539
3. Dunne M, Corrigan OI, Ramtoola, Z (2000) Influence of Particle Size and Dissolution Conditions on the Degradation Properties of Polylactide-co-Glycolide Particles. Biomaterials 21(16):1659-1668
4. Kaerger JS, Edge S, Price R (2004) Influence of Particle Size and Shape on Flowability and Compactibility of Binary Mixtures of Paracetamol and Microcrystalline Cellulose. Eur J Pharm Sci 22:173-179
5. Vankeirsbilck T, Vercauteren A, Baeyens W, Van der Weken G (2002) Applications of Raman Spectroscopy in Pharmaceutical Analysis. Trends Anal Chem 21(12):869-877
6. Chalmers JM, Edwards HGM, Hargreaves MD (eds) (2012) Infrared and Raman Spectroscopy in Forensic Science. John Wiley & Sons, Ltd., West Sussex, UK
7. Malvern Instruments (2009) Inform: Morphologically directed chemical identification- Coupling particle characterization by morphological imaging with Raman spectroscopy
8. Zona C (2006) The Development of a Protocol for the Microscopical Analysis of White Powder Unknowns: From the Hot Zone to the Microscope. Microsc Microanal 12:16-17

9. Hargreaves M, Page K, Munshi T, Tomsett R, Lynch G, Edwards HGM (2008) Analysis of seized drugs using portable Raman spectroscopy in an airport environment- a proof of principle study. J Raman Spectrosc 39:873-880
10. Ferrari A, Meyer JC, Scardaci V, Casiraghi C, Lazzeri M, Mauri F, Piscanec S, Jiang D, Novoselov KS, Roth S, Geim AK (2006) Raman Spectrum of Graphene and Graphene Layers. Phys Rev Lett 97:1-4
11. The Drug Quality and Security Act (H.R. 3204) (2013) Section 202 of the Food, Drug & Cosmetic Act. Pharmaceutical distribution supply chain. Public Law 113-54, 113th Congress.
12. Vardakou I, Pistos C, Spiliopoulou C (2011) Drugs for youth via Internet and the example of mephedrone. Toxicol Lett 201:191-195
13. Miotto K, Striebel J, Cho A, Wang C (2013) Clinical and pharmacological aspects of bath salt use: a review of literature and case reports. Drug Alcohol Depend 132:1-12
14. Every-Palmer S (2011) Synthetic cannabinoid JWH-018 and psychosis: An explorative study. Drug Alcohol Depend 117:152-157.
15. Thornton S, Gerona R, Tomaszewski C (2012) Psychosis from a Bath Salt Product Containing Flephedrone and MDPV with Serum, Urine, and Product Quantification. J Med Toxicol 8:310-313
16. Matousek P, Parker A (2006) Bulk Raman analysis of pharaceutical tablets. Appl Spectrosc 60:1353-1357
17. Leary PE (2014) Counterfeiting: A Challenge to Forensic Science, the Criminal Justice System, and its Impact on Pharmaceutical Innovation. Dissertation, CUNY Graduate Center
18. Malvern Instruments, Ltd (2015) Component specific particle characterization of the active components in pharmaceutical topical formulations. 1-4.

19. Drug Enforcement Administration (2015) DEA Issues Nationwide Alert on Fentanyl as Threat to Health and Public Safety, Available via US Department of Justice. https://www.dea.gov/divisions/hq/2015/hq031815.shtml. Accessed 01 October 2016
20. Muenter M, Sharpless N, Tyce G, Darley F (1977) Patterns of dystonia ("I-D-I" and "D-I-D") in response to l-dopa therapy for Parkinson's disease. Mayo Clin Proc 52:163-174
21. Angrist B, Gershon S (1976) Clinical effects of ampetamine and L-DOPA on sexuality and aggression. Comprehen Psychiat 17:715-722
22. Coppola M, Mondola R (2012) Synthetic cathinones: Chemistry, pharmacology and toxicology of a new class of designer drugs of abuse markted as "bath salts" or "plant food". Toxicol Lett 211:144-149
23. Dean B, Stellpflug S, Burnett A, Engebretsen K (2013) 2C or Not 2C: Phenethylamine Designer Drug Review. J Med Toxicol 9:172-78
24. Lociciro P, Esseiva P, Hayoz P, Dujourdy L, Besacier F, Margot P (2007) Cocaine profiling for strategic intelligence purposes, a cross border project between France and Switzerland: Part 1. Optimisation and harmonisation of the profiling methods. Forensic Sci Int 167:220-228
25. Theerakulpisut P, Gunnula W (2012) Exogenous Soribitol and Trehalose Mitagated Salt Stress Damage in Salt-Sensitive but not Salt-Tolerant Rice Seedlings. Asian J Crop Sci 4:165-170
26. Lowenthal W (1972) Disintegration of tablets. J Pharm Sci 61:1695-1711
27. Jarosz PJ, Parrot EL (1984) Effect of lubricants on tensile strengths of tablets. Drug Dev Ind Pharm 10:259-273

Tables and Figures:

Table 1

Raman Analysis Parameters

Laser	785 nm semiconductor, <500mW power
Optic Range	150$cm^{-1}$to 1850cm^{-1}
Spot Size	3 µm
Exposure Time	2 seconds
Number of particles	3000

Table 2

Multicomponent Drug Mixture: Particle count and volume contribution percentages for a mixture of 0.1 grams each of powdered cocaine, phenobarbitol, pentabarbitol, amphetamine and D-methamphetamine.

Drug	Particle Count Percentage	Volume Contribution Percentage
Cocaine	23.94%	11.6%
Phenobartbitol	38.09%	6.25%
Pentabarbitol	20.88%	3.31%
D-Methamphetamine	11.56%	17.30%
Amphetamine	8.93%	66.11%

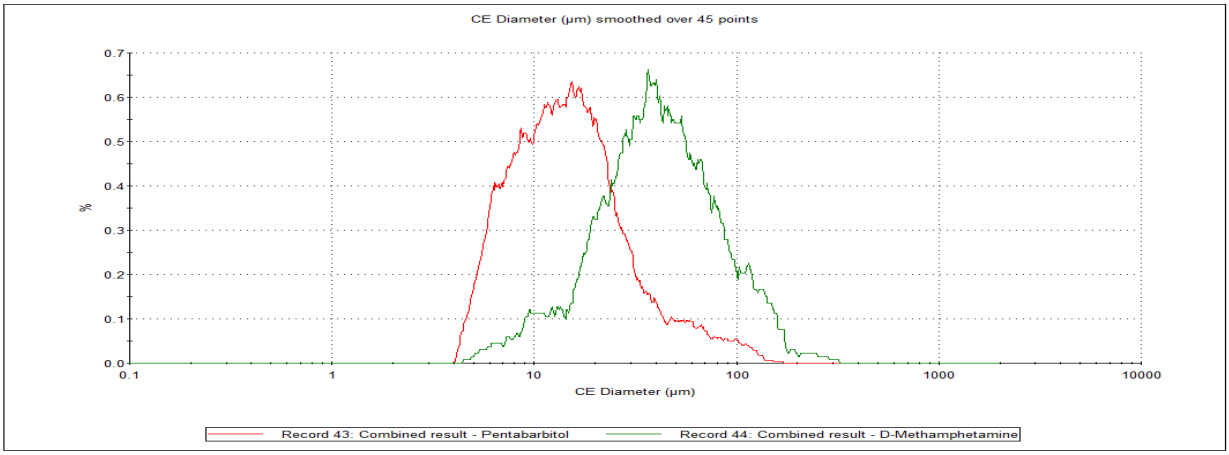


Fig. 1. Particle size distributions for phenobarbitol and pentabarbitol from the mixture of 0.1 grams each of powdered cocaine, phenobarbitol, pentabarbitol, amphetamine and D-methamphetamine: The ability to assign particle size distributions based upon chemical chemical species is possible due to the coupling of particle imaging with Raman spectral data analysis. Phenobarbitol and pentabarbitol are related compounds but have different Raman spectra and, as shown, can have very different particle size distributions. This information may be used as a means of source determination between multiple drug seizures as similar preparations of drugs found in multiple seizures may be sufficient to link them to a common source.

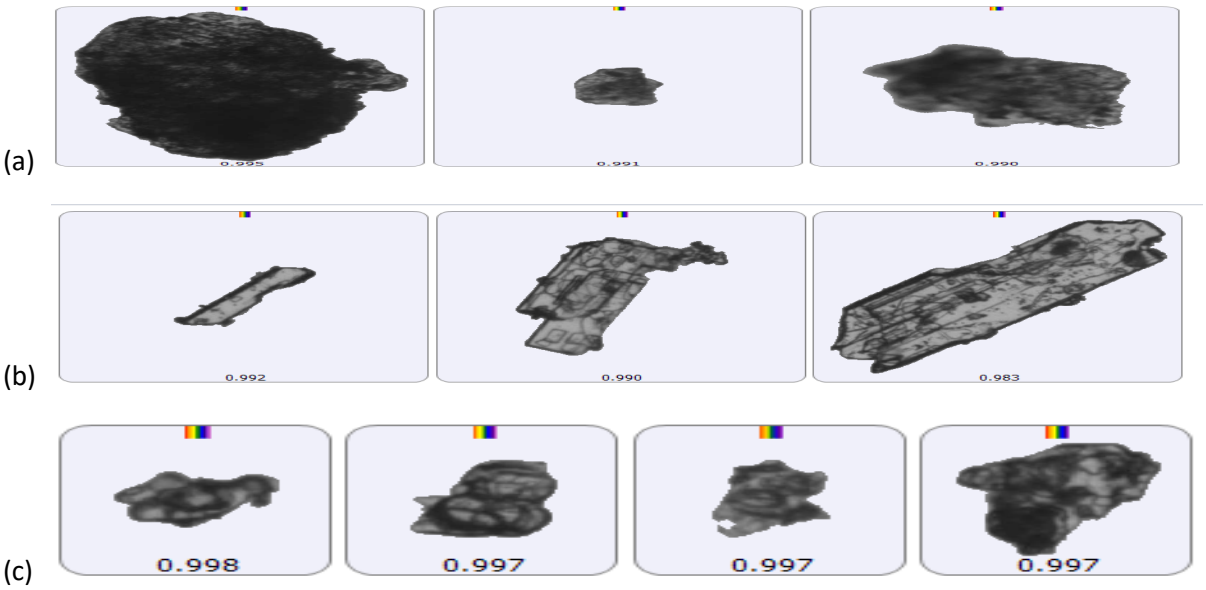


Fig. 2. Photomicrographs showing the varied particle morphologies of (a) amphetamine, (b) D-methamphetamine, and (c) cocaine from the mixture of 0.1 grams each: The particle size and shape of a substance can be useful for determination of manufacturing process and, therefore, for comparative source attribution. Different methods of preparation can result in particles with different crystal structures and habits. Usually, slow crystallization methods form larger crystals, while rapid crystallization methods form smaller crystals.

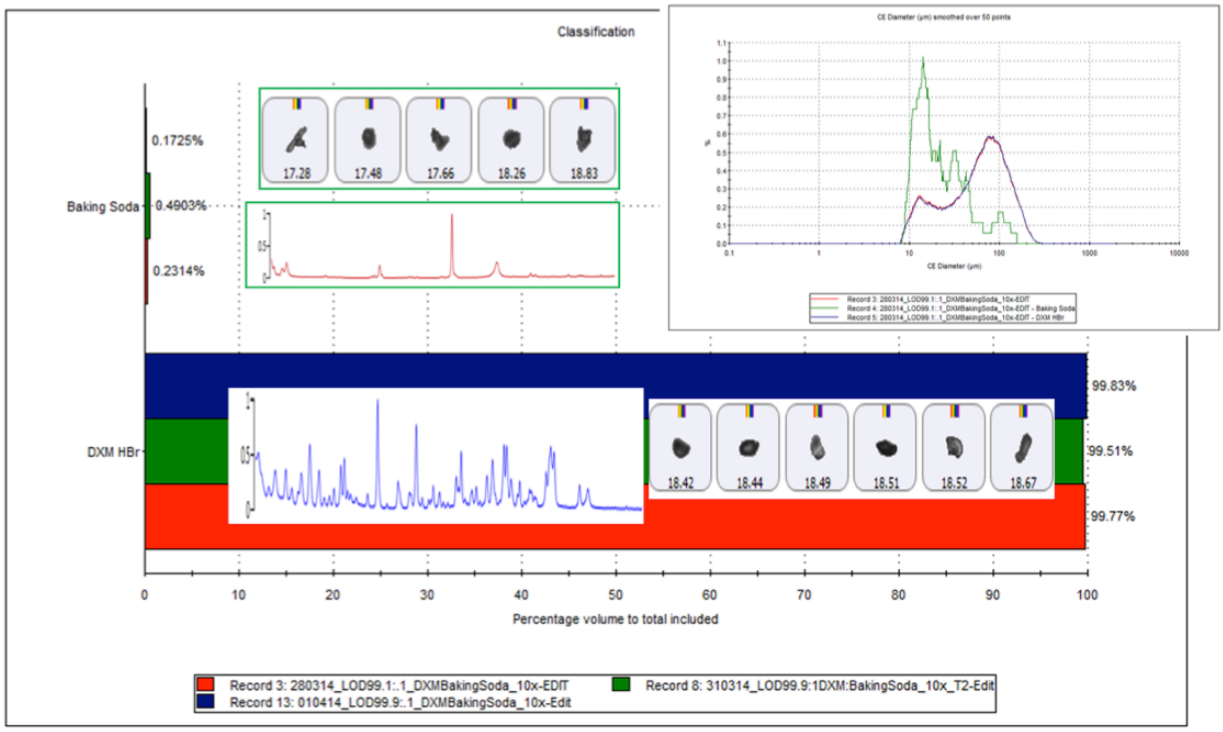
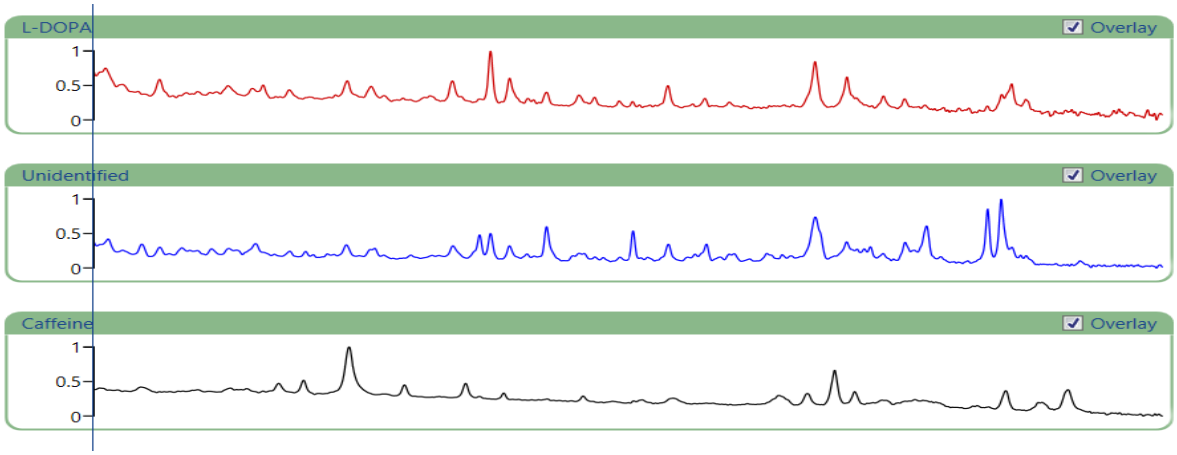
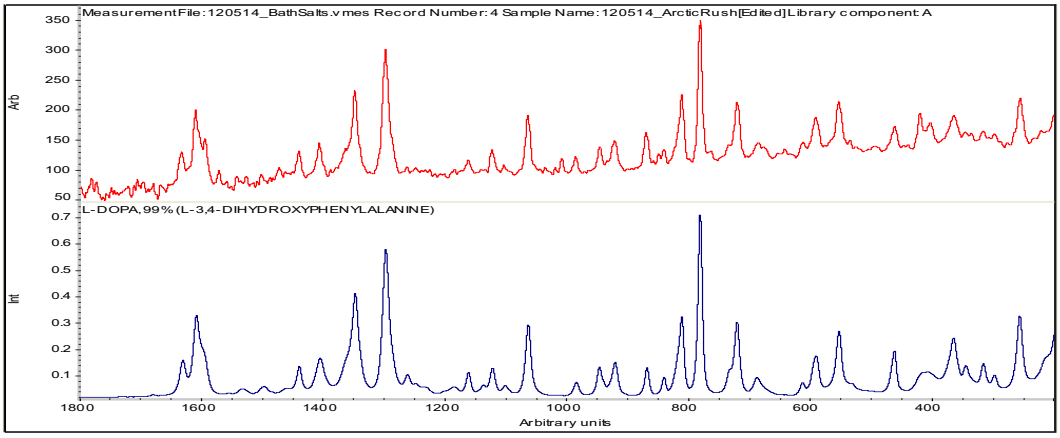


Fig. 3. Results of MDRS analysis of a sample of dextromethorphan hydrobromide (DXM) with a trace-level concentration of baking soda (999:1 by weight), completed in triplicate: Data analysis includes Raman spectral library searching, image analysis of the component particle morphologies, calculation of the percentage volume of each component, and comparison of the particle size distributions. Traditional Raman spectroscopic analysis is not capable of reliably identifying trace-level-concentration components of a mixture. In addition, manual particle picking with analysis by Raman microspectroscopy would be excessively time consuming, labour intensive, and subjective in nature. It's also possible particles for analysis could be missed. The particle size distributions for the overall blend and the bulk amount of dextromethorphan are very similar. The particle size distribution of the baking soda is different from these two. However, based upon particle size and distribution, identification of baking soda in the mixture sample would not be possible. It is the particle-specific chemical targeting provided by MDRS that enables the detection of the low-level component, and makes MDRS a very useful tool to detect trace level lacing of a drug sample. Low-concentration contaminants are commonly seen in seized drug samples; these contaminants could be attributed to either trace materials picked up through passive transfer or an additional adulterant/diluent. These contaminants could be used to determine source or origin, or for situations where small amounts of material are used to adulterate as sample as in the case of fentanyl laced in heroin (19).

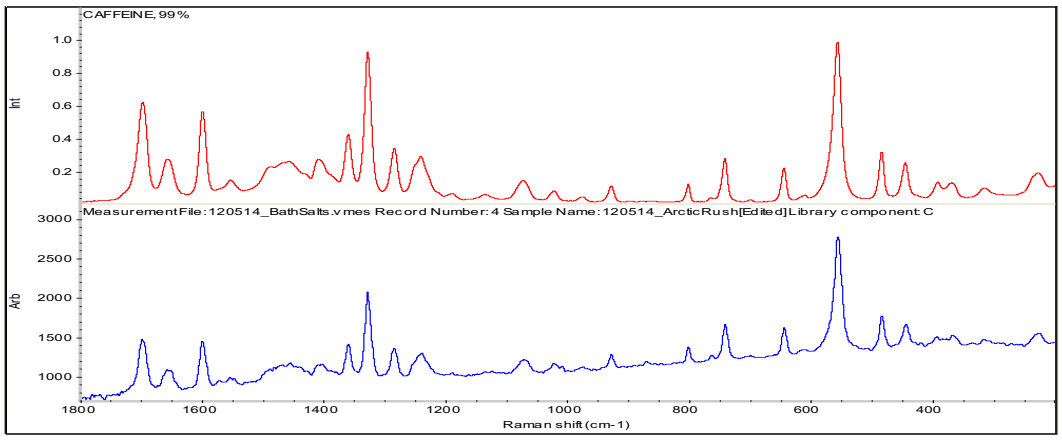


(a)



(b)

(c)



(d)

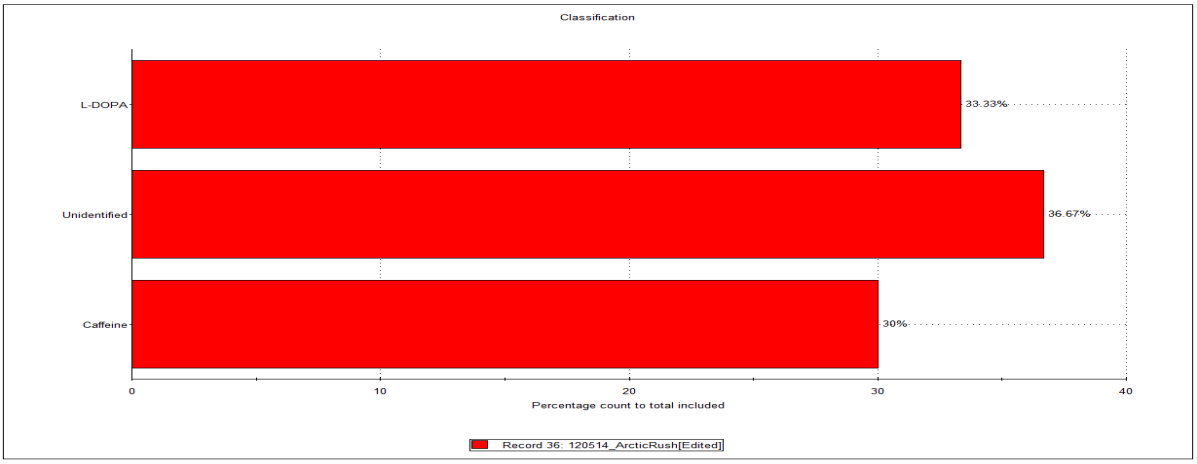
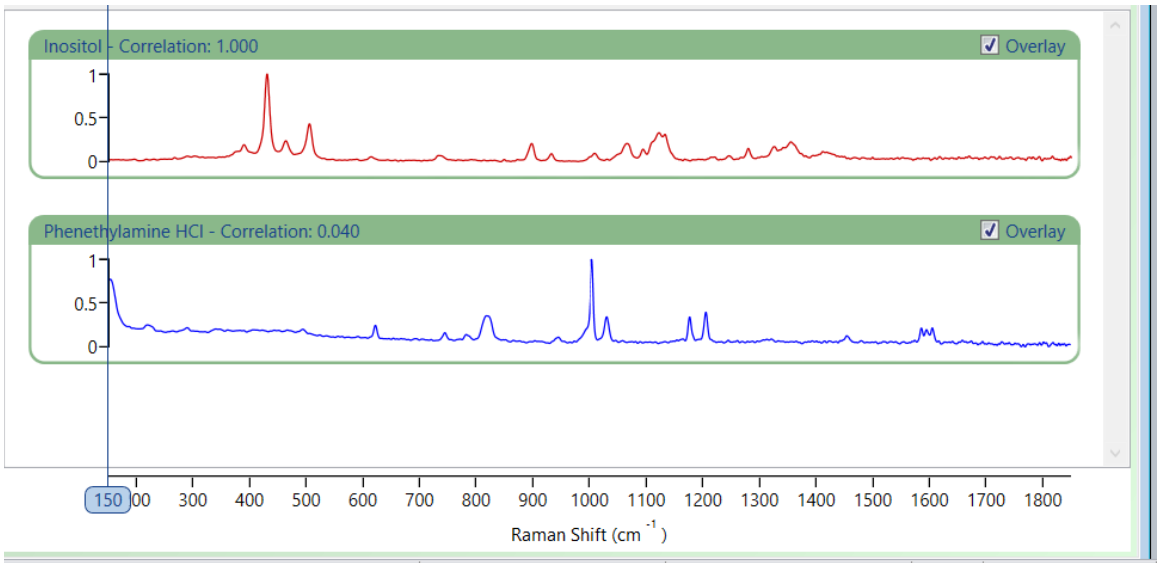
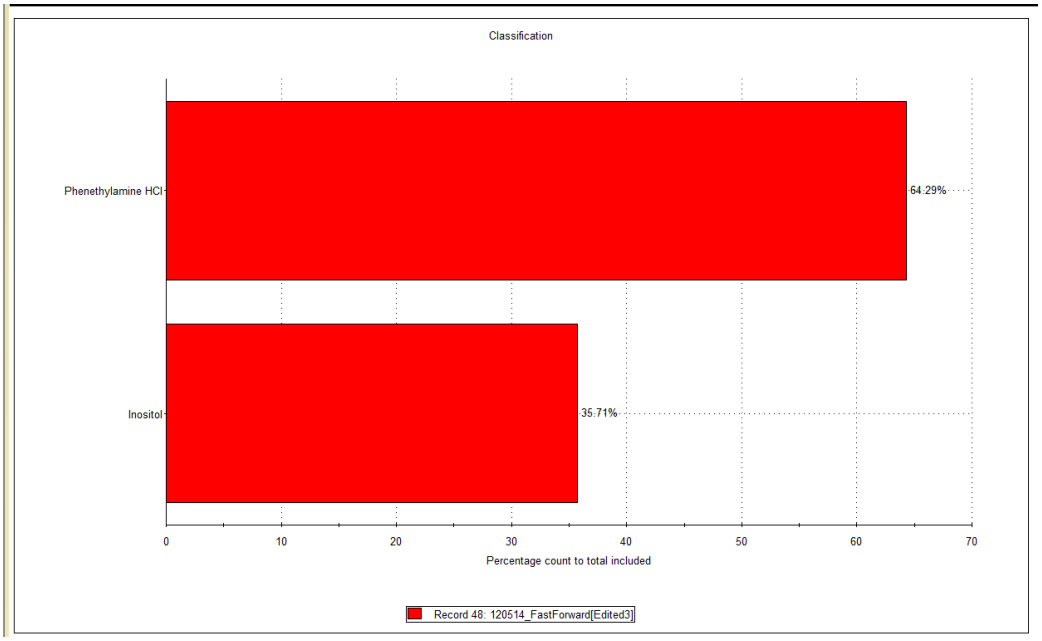


Fig. 4. MDRS results for the bath salt "Arctic Rush": (a) MDRS determined the sample to be a three-component mixture. Two of these components were spectrally matched by the library. The first was caffeine, which is commonly used as an adulterant since it is a stimulant and, therefore, useful as a cutting agent with other stimulants (9). (b) The library search correlation algorithm identified caffeine with a 99.37 hit quality. (c) The second component identified by library matching was 3,4-dihydroxyphenylalanine, commonly known as L-DOPA. The library search correlation algorithm identified L-DOPA with a 94.97 hit quality. L-DOPA is commonly used for the treatment of patients with Parkinson's Disease. L-DOPA crosses the blood-brain barrier and is converted to dopamine, which activates the pleasure and reward centers of the brain (20). There have been cases of people abusing L-DOPA as a means of enhancing the dopamine rush, which would explain why it would be found in a mixture that people would be taking to induce euphoria. It has been shown to increase aggressive behavior when taken in conjunction with methamphetamine (21). (d) A graph of the percentage count for each of the three components of the mixture, which could be used to compare samples from different seizures for common source attribution.



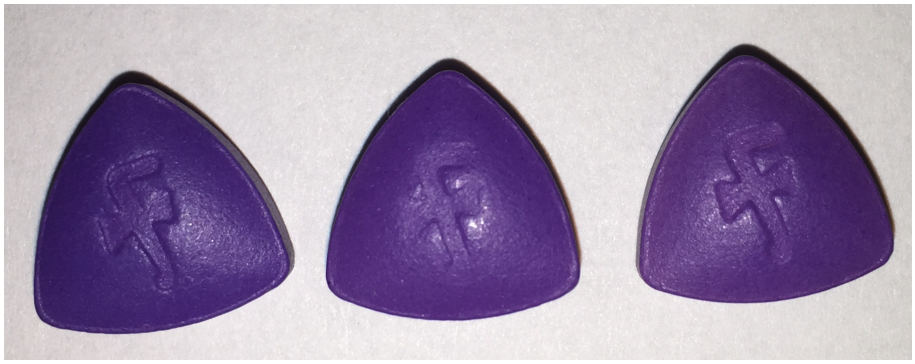
(a)



(b)

Fig. 5 MDRS results for the bath salt "Fast Forward": (a) Fast Forward contained a mixture of inositol and phenethylamine. This product was not advertised as a bath salt, which was a legally valid statement. This is because phenylethylamine and the structure of synthetic cathinone differ slightly from each other. Phenethylamine has a keto group on the beta carbon of the amino alkyl chain connected to the phenyl ring (22). This keto group is absent in typical synthetic cathinone. Regardless of the slight difference, the two share very similar effects to the end user, often ending in a state of excited psychosis or death (23). Inositol is a sugar alcohol that commonly is used as cutting agent for narcotics (24), in addition it is also added to roads as a means to counter the harmful effects of road salt (25).

(a)



(b)

Fig. 6. Photographs of the (a) front and (b) back of the three purchased samples of Fildena. The left two pills originated from Singapore and the sample on the right came from India. All three pills are visually similar, making discrimination based on a macroscopic examination unlikely.

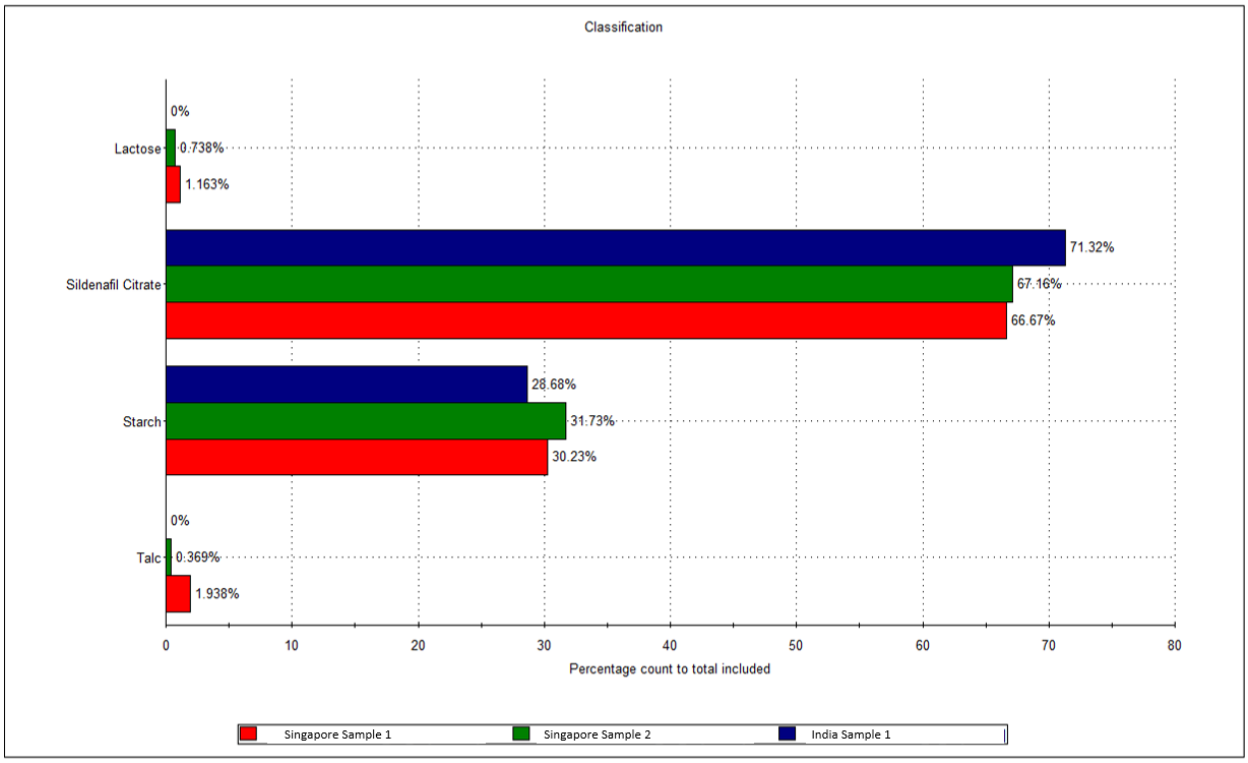


Fig. 7. The percentage counts of the mixture of components of the three counterfeit Fildena samples: All of the analyzed samples contained sildenafil citrate, which is the active ingredient in the authentic branded Pfizer product Viagra. These samples had been previously analyzed and were found to have a lower concentration of sildenafil citrate than authentic Viagra samples (17). In addition to the active, starch was present in all samples. Starch is a commonly used binder in pharmaceuticals (26). Also, the two pills produced in Singapore contained a small concentration of lactose and talc, both of which are commonly used as inert filler adulterants to make up the weight of a final dosage form (27). Both of these compounds are in low concentrations when compared to the sildenafil citrate, and it is very likely these binders would be missed with traditional Raman analysis. Trace-level compounds such as these could be instrumental in determining the manufacturer, be used to link a sample to a specific location, or determine if there are dangerous compounds present in the sample. In addition, ratios of components present in the sample may differ based indicating that they do not have a common source. The sample from India contained only the sildenafil citrate and starch, with no other components. By comparing both the chemical composition and the particle size distributions, counterfeit seizures can be evaluated to determine if they could come from a common source.