

Drug Analysis

International Edition: DOI: 10.1002/anie.201910177

German Edition: DOI: 10.1002/ange.201910177



Analysis of Powders Containing Illicit Drugs Using Magnetic Levitation

Christoffer K. Abrahamsson, Amit Nagarkar, Michael J. Fink, Daniel J. Preston, Shencheng Ge, Joseph S. Bozenko, Jr.,* and George M. Whitesides*

Abstract: Magneto-Archimedes levitation (MagLev) enables the separation of powdered mixtures of illicit drugs (cocaine, methamphetamine, heroin, fentanyl, and its analogues), adulterants, and diluents based on density, and allows the presumptive identification of individual components. Small samples (mass < 50 mg), with low concentrations of illicit drugs, present a particular challenge to analysis for forensic chemists. The MagLev device, a cuvette containing a solution of paramagnetic gadolinium(III) chelate in a non-polar solvent, placed between two like-poles-facing NdFeB magnets, allowed separation of seven relevant compounds simultaneously. In particular, initial separation with MagLev, followed by characterization by FTIR-ATR, enabled identification of fentanyl in a sample of fentanyl-laced heroin (1.3 wt % fentanyl, 2.6 wt % heroin, and 96.1 wt % lactose). MagLev allows identification of unknown powders in mixtures and enables confirmatory identification based on structure-specific techniques.

Introduction

Herein, the use of Magneto-Archimedes levitation (MagLev)^[1] is described for the separation, and measurement of the density and abundance of, compounds in mixtures of powdered illicit drugs (for example, fentanyl, heroin, cocaine, and methamphetamine hydrochlorides), together with adulterants and diluents.^[2] Our analysis focuses on the psycho-

active components in these mixtures of drugs (the so-called active compounds). We are especially interested in fentanyl and its analogues, for which we used MagLev as a technique that both provides presumptive (that is, tentative) identification of the compounds (based on density) and facilitates subsequent identification by other techniques. Combining MagLev (to separate mixtures, and to allow presumptive identification) and molecular spectroscopy (using whichever technique is most appropriate) for molecular identification provides a method of confirming the identity of drugs in mixtures (Figures 1 and 2; Supporting Information, Movie S1). The different levels of assurance in identification are discussed later. These methods are particularly useful when analytical methods must be rapid and simple (for example, in screening at forensic laboratories, and in the field) and the active compound is dilute (0.1–5.0 wt %), as is often the case for fentanyl and its analogs in street-level drugs.^[2b] We define dilution of powders as the process of mixing one or more powders with each other to achieve a reduction of the relative content of one or more compounds (and consequently, to increase of the volume of the drug-containing mixture to facilitate handling). We used a type of MagLev device that we have described previously (Supporting Information, Figure S1).^[3] The design of all experiments and relevant theory is described in the Supporting Information.

The abuse of drugs is a major public health problem, with fatalities attributed to overdoses numbering 7600 in the European Union (EU) (78 % involving opioids) and 70000 in the United States (US) (86 % opioids) in 2017.^[2] A potent subgroup of these compounds are the synthetic opioids (mainly fentanyl and its analogues) that were involved in 30000 deaths in the US.^[2b,c] Opioids are defined as molecules that interact with the opioid receptors in neural and intestinal cells,^[4] opiates are opioids of natural or semi-natural origin;^[5] relevant molecular structures are summarized in the Supporting Information, Table S1.

Fentanyl, a painkiller and anesthetic that is widely used in medicine, has particular relevance in law enforcement because it is the predominant synthetic opioid found in seized samples of drugs of abuse.^[2b,c] Fentanyl and its analogues can be orders of magnitude more potent than natural opioids; for example, the activities of these compounds in suppression of pain, relative to morphine, are: morphine (potency defined as 1 ×), oxycodone (1.8 ×), acetyl fentanyl (16 ×), fentanyl (100 ×), and carfentanyl, (10000 ×).^[2c,4,6] These compounds are mainly used as additives in products that are marketed in street drugs as heroin and cocaine.^[7] An addict will typically use 0.3–1.0 mg of fentanyl to achieve a high; a dose of 2.0–

[*] Dr. C. K. Abrahamsson, Dr. A. Nagarkar, Dr. M. J. Fink, Dr. D. J. Preston, Dr. S. Ge, Prof. G. M. Whitesides
Department of Chemistry and Chemical Biology
Harvard University (USA)

E-mail: gwhitesides@gmwgroup.harvard.edu

Homepage: <https://gmwgroup.harvard.edu/>

J. S. Bozenko, Jr.

Special Testing and Research Laboratory

Drug Enforcement Administration (DEA)

Dulles, VA (USA)

E-mail: jsbozenko@dea.usdoj.gov

Prof. G. M. Whitesides

Wyss Institute for Biologically Inspired Engineering

Harvard University

60 Oxford St., Cambridge, MA 02138 (USA)


and

Kavli Institute for Bionano Inspired Science and Technology

Harvard University

29 Oxford Street, Cambridge, MA 02138 (USA)

 Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:

 <https://doi.org/10.1002/anie.201910177>.

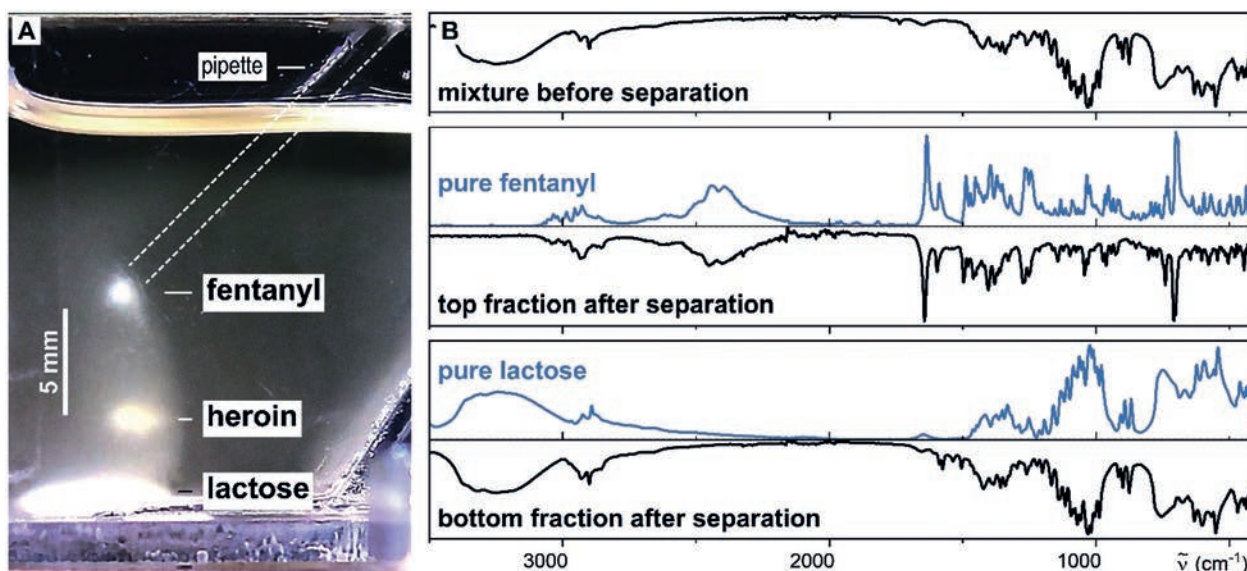


Figure 1. Successful separation, presumptive identification, and confirmatory identification of dilute fentanyl, in a mixture of heroin and a diluent (lactose). A) An image taken after 30 min of separation by MagLev of a powdered mixture of fentanyl-containing heroin (fentanyl-HCl (1.3 wt%), heroin-HCl (2.6 wt%), and α -lactose (96.1 wt%)). The separation was performed in a custom-made cuvette (shaped to allow easy entry of a pipette) filled with a paramagnetic solution of $\text{Gd}(\text{DPM})_3\text{TOPO}$ (450 mM) in a mixture of 23 vol% hexane and 77 vol% tetrachloroethylene. The image was uniformly post-processed for contrast and clarity; the original image is in the Supporting Information, Figure S11. B) The separated fractions were extracted using a Pasteur pipette, and were subsequently rinsed with hexane under suction filtration to remove any remaining gadolinium complex and air-dried. FTIR-ATR spectra (normalized to the highest peak) were measured from the powdered mixture before separation (top spectrum). The extracted fractions containing fentanyl and lactose (lower two black lines), and the pure compounds (blue lines) are below.

5.0 mg may cause death.^[8] In the US (2017), the Drug Enforcement Administration (DEA) found that the average content of fentanyl in drugs obtained from street-level retail was 5.1 wt% (with a total range of 0.1–97.8 wt% for all confiscated drugs).^[2b] Fentanyl hydrochloride is the prominent fentanyl salt in seized samples, while the citrate salt is found in a minority of confiscated drugs.^[2b] Common ranges of concentrations for other illicit drugs at the retail level are listed in the Supporting Information, Table S2.

To moderate potency, and to increase profit margins, drugs are commonly diluted with adulterants, that is, semi-active compounds that are added to enhance the effect of the drugs or simply mimic their properties. For example, because drug users test the bitterness of mixtures to judge the content of heroin, acetaminophen and caffeine are added to maintain the bitterness of the mixture when heroin, which is bitter, is diluted. Diluents (non-active compounds, such as lactose, dimethyl sulfone, and glucose) are added to lower the concentration of the drug and to make it easier to handle and use.^[9]

To identify a drug according to forensic standards of analysis, two to three different analytical methods must be used (techniques are listed in the Supporting Information, Table S3; combinations of techniques of different ranking can be used to establish the composition of mixtures).^[10] Techniques with molecular specificity (X-ray diffractometry and IR, NMR, Raman, and mass spectrometry) are given the highest ranking. GC-MS is the workhorse in modern forensic drug laboratories (in most US federal, state, and municipality laboratories, depending on the state),^[11] but the cost, the lack

of portable systems, and the technical skill needed to handle this instrument prohibit large-scale use in the field. Most separations (CE, GC, LC, and other less-molecularly-specific techniques) are considered intermediate in value for identification. Other methods that provide limited information about the molecular structure are in the third, lowest, category. When an appropriate combination of methods is used to confirm the presence of a compound (for example, at least two techniques, with one from category A and the second from categories A, B, or C, or, alternatively, three techniques if at least two are from category B and the additional technique is from B or C^[10]), and when the sampling procedure adheres to defined protocols, only then is the presence of the compound considered to have been identified.^[10] This level of identification is referred to as confirmatory identification (see the Supporting Information, Table S3 for a more detailed description).

In the US, confirmatory identification can only be performed by an expert (for example, a forensic chemist); a police officer cannot be admitted as an expert witness in court for chemistry or forensics and, therefore, the opinion of the police officer cannot be entered as fact;^[12] thus, a measurement performed by a law enforcement officer with a confirmatory technique is assigned a standing similar to that of a presumptive technique.^[13] However, the use of techniques of high molecular specificity by law enforcement officers have the benefit of reducing the number of false positive and negatives that are inherent to most other presumptive identification techniques.

MagLev has the potential to be used for presumptive identification, based on compound density. Presumptive identification is the lowest level of specificity (Category C in the Supporting Information, Table S3), but encompasses the most common group of analytical methods used to screen compounds in the field (outside of an analytical laboratory). Immunoassays^[14] and colorimetric tests^[15] are other examples; these techniques provide weak evidence of molecular identity, but are easily used in resource-limited circumstances (for example, border inspection stations and mail-sorting facilities). MagLev has, however, the potential to enable more specific techniques because of its ability to separate dilute compounds in mixtures of powders.^[10,15] We stress here that MagLev has not been evaluated or approved by any forensic organization^[10] for analysis of seized illicit drugs; however, we suggest that the MagLev could, after further development, become a candidate for evaluation.

Results and Discussion

We demonstrate that MagLev can be used to determine three characteristics of a powdered sample: 1) the minimum number of compounds present in the sample; 2) the densities of these separately levitating compounds (or mixtures of overlapping compounds) (Figure 1 and Figure 2); and 3) qualitatively, an estimate of the relative amounts of these compounds (Figure 3D). To finish the presumptive identification, the densities measured for the levitating fractions are compared with reference materials (pure compounds) using a look-up table (Supporting Information, Table S4). MagLev generates more information from the same sample than most techniques used for presumptive identification and can measure the density of multiple compounds, including those present in small amounts, for a range of chemical structures in a one-step procedure. More importantly, it both allows the separation and isolation of the compounds present in a mixture, and facilitates an increase in the specificity of more detailed spectroscopic methods.

Determining the composition of illicit drugs in the field faces at least four hurdles: 1) the technical and procedural training required to ensure correct handling of the sample; 2) access to appropriate instruments; 3) the risk of exposure to the drugs; and 4) the highly variable composition of the drug mixtures.^[16] For these and other reasons, seized samples are often not analyzed for their constituents in the field, but only later at a local law enforcement facility, or at a well-equipped and competently staffed central laboratory. Shipping to, and analysis in, central laboratories can introduce long delays in the identification of molecular constituents of mixtures of drugs (for example, backlogs in analysis are common).^[17]

Mixtures of illicit drugs can contain a wide range of compounds. With this in mind, we demonstrated separation of active compounds (with a range of chemical properties) commonly found in samples seized by law enforcement, including the hydrochloride salts of fentanyl, acetyl fentanyl, cocaine, heroin, and methamphetamine (Figure 1 and Figure 2). Five relevant powdered mixtures were separated, each

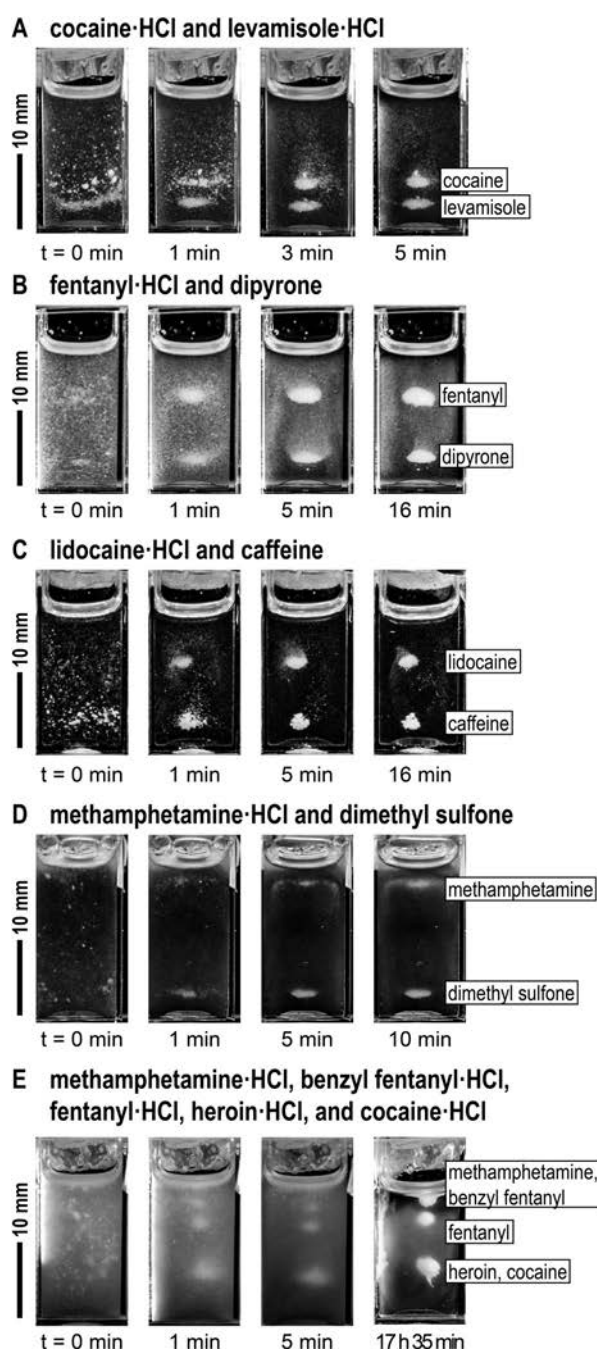


Figure 2. Time-lapse photographs of the separation of mixtures of powdered illicit drugs, adulterants, and diluents (2.5–9.5 mg of each compound) using MagLev. The paramagnetic solution used in the device was Gd(DPM)₃TOPO (450 mM) dissolved in a mixture of 23 vol% hexane and 77 vol% tetrachloroethylene. Photographs were uniformly post-processed for contrast and clarity; the original images are in the Supporting Information, Figure S11.

composed of commonly encountered active compounds, adulterants, or diluents (Figure 1 A, and Figure 2). Although cocaine·HCl (1.32 g cm⁻³) and heroin·HCl (1.34 g cm⁻³) did not separate completely under the conditions we described here (Figure 2 E; Supporting Information, Table S4), their separation by density can easily be improved by changing a number of parameters described elsewhere.^[18] In any event,

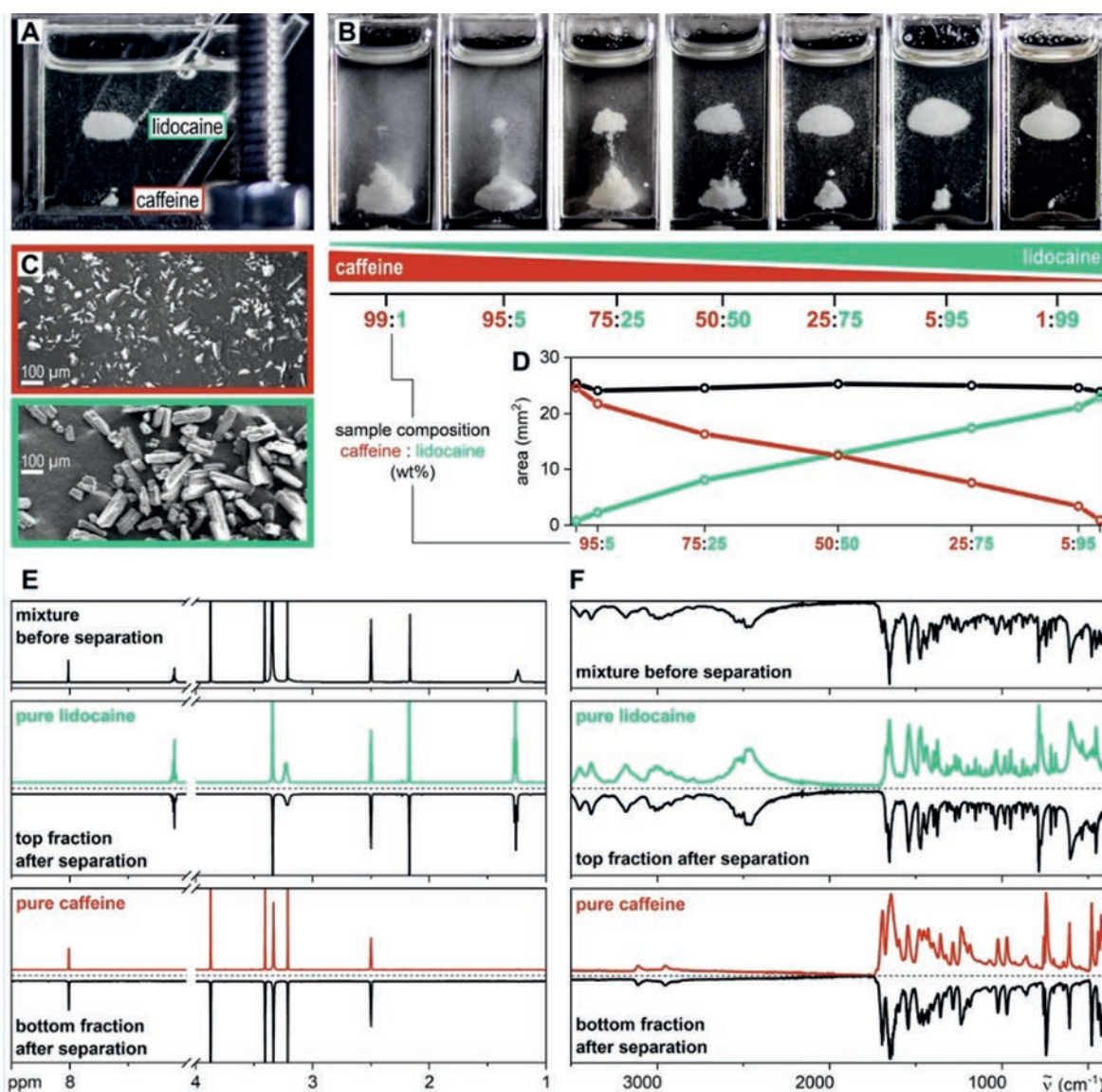


Figure 3. A model system for the investigation of MagLev separation of powdered mixtures and the following characterization with spectroscopic techniques. A) MagLev separation (30 min) of a mixture of lidocaine-HCl and caffeine (95:5 wt%; 50 mg) in a cuvette filled with the paramagnetic solution, and extraction using a Pasteur pipette. B) MagLev separation (20 min) of powdered mixtures (50 mg) of lidocaine-HCl (top clouds) and caffeine (bottom clouds) in different proportions (wt%). The paramagnetic solution in (A) and (B) consisted of Gd(DPM)₃TOPO (450 mM) dissolved in a solvent mixture of 23 vol% hexane and 77 vol% tetrachloroethylene. Height of cuvettes: 25 mm. C) Scanning electron micrographs of crystals of lidocaine-HCl and caffeine (pure compounds). D) The projected, two-dimensional areas of the levitating fractions of lidocaine-HCl (green line) and caffeine (red line), and their combined area (black line), are plotted against the chemical composition of mixtures. The area was measured in images with a physical ruler for reference of distance with the software ImageJ. E) ¹H-NMR (600 MHz) characterization of a mixture (50 mg) of lidocaine-HCl and caffeine (50:50 wt%) and the fractions after separation (30 min) in the MagLev; for clarity, some signals were clipped, and some regions omitted. The individual fractions were extracted as in (A) and rinsed with hexane during suction filtration and air-dried on a filter paper. Part of the residue (3.0 mg) was dissolved in [D₆]DMSO (0.6 mL)-no lidocaine was detected with ¹H-NMR in the caffeine-rich fraction, and no caffeine in the lidocaine-HCl-rich fraction. Signals from the solvent DMSO (at 2.5 ppm) and water (at 3.3 ppm) are present. F) FTIR-ATR characterization (normalized to highest peak) of the samples purified in (E) except that the residue was characterized as a dry powder. Pure compounds were used as controls for both the ¹H-NMR and FTIR-ATR characterization. Photographs in (A) and (B) were uniformly post-processed to enhance contrast and clarity; the Supporting Information contains the originals.

the combination of cocaine-HCl and heroin-HCl is not common in street-level drugs.^[19]

The synthetic opioids can be especially challenging to detect owing to their high potency, which enables (and requires) high dilution (≤ 5 wt%) of the active components and thus makes the analyses of these opioids in small samples

(≤ 50 mg) particularly difficult (a fentanyl compound may, for example, be present only as a few crystals in a 50 mg sample).

Previously published or widely deployed portable methods for detection of fentanyl include colorimetric tests,^[15,20] microcrystalline tests,^[21] electrochemistry,^[22] immunochemistry,^[14] near-infrared spectroscopy,^[23] surface-enhanced Raman

spectroscopy,^[24] Raman spectroscopy,^[25] and FTIR spectroscopy.^[26] The most common portable methods used in the field by law enforcement personnel for general detection of drugs are colorimetric tests,^[15,20] handheld Raman (such as Thermo Scientific TruNarc or Chemring Detection Systems PGR-1064),^[25] and FTIR (such as Thermo Scientific TruDefender FTXi and Smiths Detection HazMatID Elite.)^[27] (Portable methods of drug detection are reviewed by Kranzler et al.,^[28] Harper et al.,^[17b] and de Araujo et al.^[29]) Both Raman and FTIR-ATR, which are considered more sensitive and accurate than colorimetric tests, have limits-of-detection of approximately 5 wt %, and are therefore not sensitive enough to detect dilute drugs directly in the mixtures of illicit drugs, adulterants, and diluents.^[17b,25,30]

We demonstrated that MagLev can separate dilute (1.0–2.6 wt %) compounds from powdered mixtures, including: 1) 1.3 wt % fentanyl-HCl, 2.6 wt % heroin-HCl, and 96.1 wt % α -lactose (Figure 1; Supporting Information, Figure S4); 2) 1.0 wt % lidocaine-HCl and 99.0% caffeine (Figure 3B); and 3) 99.0 wt % lidocaine-HCl and 1.0 wt % caffeine (Figure 3B). FTIR-ATR could not detect the presence of fentanyl-HCl in the first mixture before separation of the mixture, but it provided clear confirmatory identification of fentanyl-HCl in the fraction having the expected density (as compared to pure fentanyl) for fentanyl-HCl after separation (Figure 1B). The lower limit in concentration for a component of mixture that can be separated by MagLev is below 1 wt % (Figure 3B).

The separation of lidocaine-HCl from caffeine (Figure 3), used here as model constructed from easily accessible, low-risk, but relevant adulterants, demonstrates that MagLev can facilitate identification of dilute compounds in powdered mixtures by separating these fractions (as few as five 100–200 μm crystals, circa 0.1 mg) from other compounds in 50 mg samples consisting of hundreds to thousands of particles of other compounds (Figure 3B).

This model system facilitated the development of MagLev for uses with powdered mixtures of illicit drugs, and also for the investigation of the dynamics of separation of particulates in a MagLev device (for more details about the choice of model system, see the Supporting Information, Section 3.9). MagLev separated the binary mixtures of lidocaine-HCl and caffeine of seven different compositions into two fractions, as expected, and the amount of compounds in each fraction (quantified by image analysis, Figure 3D) agreed quantitatively with the known compositions of the samples. The size of the crystals influenced the kinetics of separations: both compounds consisted of rod-shaped crystals (Length of crystals (Figure 3C): a) lidocaine—minimum 20 μm ; quartile 1st 61 μm , 2nd 92 μm , and 3rd 135 μm ; maximum 292 μm . b) caffeine—minimum 4 μm ; quartile 1st 12 μm , 2nd 18 μm , and 3rd 28 μm ; maximum 89 μm ; $n = 200$); caffeine, however, is present mostly as large aggregates (500–2000 μm , by visual estimation from Figure 3B) that consist of small crystals.

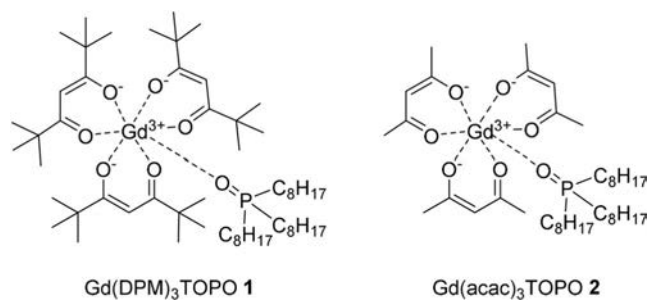
MagLev separated crystals of both compounds within approx. 20 min, but some non-aggregated (small) particulates of caffeine remained suspended after this period (observed as less transparent paramagnetic solutions in samples of high (≥ 75 wt %) caffeine content), which is due to the high ratio of

drag-to-magnetic-force^[18c] for small particles. The time of separation of the illicit drugs (Figure 2) were comparable to that of caffeine or lidocaine, indicating that the particle sizes found in the powders of the illicit drugs are of a similar range.

Following separation using MagLev, the fractions were extracted and characterized by NMR (Figure 3E) and FTIR-ATR (Figure 3F); the close match of the spectra of the extracted fractions to the standards (pure compounds) suggests excellent separation of crystals of these two compounds using MagLev. We presume the separation is near complete; residual crystals due to incomplete separation may still be present in the fractions but are at or below the limit-of-detection of either spectroscopic method. The separation with MagLev also enabled unambiguous identification of caffeine with FTIR-ATR—this compound could not be identified in the mixture before separation (Figure 3F).

We have used MagLev to measure the densities of 23 relevant compounds (6 active compounds, 10 representative adulterants and 9 diluent) found in mixtures of powdered drugs (Figures 1, 2; Supporting Information, Figure S5 and Table S4). Most compounds reached their equilibrium positions in the MagLev device in 5–30 minutes (Figure 2; Supporting Information, Figure S5), depending on the size of the grains or crystals.

MagLev cannot be performed on dissolved compounds in a solution, only on suspended objects or particles. Most illicit drugs, adulterants, and diluents are readily water-soluble (with the notable exceptions of cocaine, phencyclidine, and heroin in their base forms);^[31] thus, their separation and analysis with MagLev requires non-polar paramagnetic solutions to suspend and levitate them. Few highly paramagnetic chelates are soluble at high concentration in non-polar solvents, while still maintaining a low viscosity of the solution.^[18b] In this study, we used mixtures of hexane ($\rho = 0.66 \text{ g cm}^{-3}$) and tetrachloroethylene ($\rho = 1.62 \text{ g cm}^{-3}$) as the solvent for the gadolinium(III) chelate complexes, because mixtures of these solvents span the range of densities needed for analysis of powdered drugs, and have suitable characteristics for the application described here (low polarity, appropriate density, low viscosity, and toxicities acceptable for these uses; see the Supporting Information, Section 3.5). We have synthesized and used compounds **1** and **2** (Scheme 1; Supporting Information, Scheme S1 outlines their syntheses, Figure S6 depicts their characterization using FTIR-ATR, and in Figures S7, S8, and Table S5 we determine their



Scheme 1. Structures of gadolinium chelate complexes used in this study.

magnetic susceptibilities using the Evans method). Compound **1** has been synthesized before,^[32] but not compound **2**. None of the compounds (illicit drugs, adulterants, or diluents) we investigated (Supporting Information, Table S2) dissolved in the non-polar paramagnetic solutions we used, as judged by eye (Figures 1 A, 2, 3; Supporting Information, Figure S5).

MagLev makes it possible to carry out presumptive identification of multiple compounds simultaneously (Figure 4; Supporting Information, Movie S2), and thus to

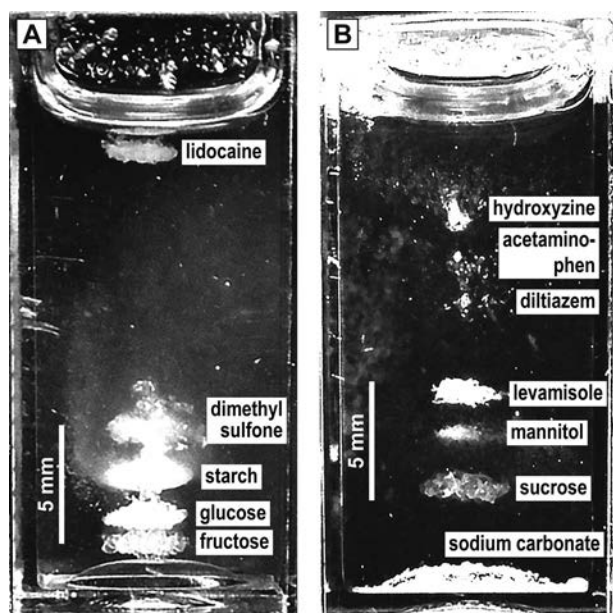


Figure 4. Separations of powdered mixtures (50–60 mg) of adulterants and diluents using MagLev. A) Lidocaine-HCl, dimethyl sulfone, potato starch, D-(+)-glucose, and β-D(-)-fructose in a solution of Gd-(DPM)₃TOPO (450 mM) dissolved in tetrachloroethylene. B) Hydroxyzine-2HCl, acetaminophen, diltiazem-HCl, levamisole-HCl, D-mannitol, sucrose, and sodium carbonate (at bottom) separated in a paramagnetic solution of Gd(acac)₃TOPO (1100 mM) in tetrachloroethylene. The densities of the levitating compounds are listed in the Supporting Information, Table S4. Photographs were uniformly post-processed for contrast and clarity; the Supporting Information, Figure S11 contains the originals.

increase the likelihood of a correct identification of the components (using a lookup table of known densities for reference) in samples, because certain combinations of drugs and/or adulterants are more common than others. For example, methamphetamine is commonly found in binary powdered mixtures with dimethyl sulfone.^[33]

For powdered mixtures of illicit drugs, a mixture of five to twelve compounds in one sample represents a worst case, but is not uncommon.^[31a]

Figure 4B demonstrates application of MagLev in the simultaneous separation of seven different adulterants and diluents from a powdered mixture. Most compounds in powdered mixtures of illicit drugs have densities in the range of 1.10–1.58 g cm⁻³ (Supporting Information, Table S4). The procedure for MagLev used in this study can measure a larger range of density (that is, 0.60–1.77 g cm⁻³; Supporting Information, Figure S9). Sodium carbonate (2.54 g cm⁻³)^[34] and

talca (2.84 g cm⁻³)^[35] are the only diluents that are routinely encountered by law enforcement that did not levitate because their densities fell outside of the allowable range. We have, in other work, demonstrated methods for levitation of objects with densities much higher than these.^[36]

The densities of compounds determined by MagLev largely agree with values reported in the literature (Supporting Information, Table S4), which were measured by XRD and calculated from the dimensions and occupancy of the unit cells, or by gas pycnometry. Our density measurements deviated from literature values by less than 20.2%. We recorded the largest differences for the hydrochlorides of methamphetamine (20.1%), levamisole (10.7%), procaine (6.0%), cocaine (5.6%), and diltiazem (4.8%). These differences may be due to impurities or different forms of the drug present in samples (for example, as hydrates, solvates, or carbonates, admixture with other compounds with similar density, particles that are partly amorphous instead of fully crystalline, crystals that included polymorphs, or other issues). Nonetheless, these differences in density are largely irrelevant for separations, as long as the compounds do separate. The values of densities for relevant compounds can, however, be important for the presumptive identification of compounds that have not been previously separated by MagLev, and should be better established (both in pure samples, and as encountered in different mixtures of illicit drugs).

To minimize errors, for compounds that have been previously characterized and that have been documented in look-up tables, we recommend that density-based presumptive identification with MagLev be performed under the same set of conditions (for example, type of MagLev device, type of paramagnetic chelate complex, and concentration of solution) used for previous characterizations.

Conclusion

MagLev is simple to use and portable. It thus offers a new method for screening drugs outside of a well-equipped forensic laboratory (for example, at crime scenes and law enforcement sites). Because separation by MagLev is rapid, it could shorten the time required for presumptive identification of illicit drugs at crime scenes. Complementary and more precise techniques could subsequently be used for confirmatory identification, because MagLev is non-destructive. The synergy of MagLev with FTIR-ATR is attractive for analysis of drugs because both techniques are portable, require little training to use, and work well with powdered compounds. The two are also complementary because MagLev compensates for the low sensitivity of FTIR-ATR in complex mixtures, by separating and concentrating fentanyl or other compounds of primary interest. One drawback of MagLev is that it requires a liquid (the paramagnetic suspending solution); this requirement makes it operationally more complex than those techniques that require only solids. Fortunately, uses of MagLev in this type of application can be optimized in the laboratory using easily obtained compounds, for example, lidocaine-HCl and caffeine, that are relevant to illicit mixtures of drugs, as components of model systems, and can thus avoid

the often prohibitive regulations placed on the use of most active compounds (Supporting Information, Schedule I and II; see Table S6).

Producers of illicit drugs make new analogues more quickly than these compounds can be scheduled as illegal compounds.^[7] Before a drug can be scheduled, multiple agencies must determine if it has a strong index of suspicion. For example, for synthetic opioids, there must be a strong suspicion that the drug causes miosis, depressed respiration, changes in mental status, and additional signs of opioid toxicity.^[4,37] A strength of MagLev (but also, in some ways, a drawback) is that the method is non-specific to the molecular structure or the biological activity; an additional, more structure-specific technique (FTIR or Raman spectroscopy, or mass spectrometry) may be required to enable the assignment of new compounds to a class. This characteristic also makes MagLev suitable for providing a rapid early warning of a new or unfamiliar compound whose density (and probably structure) varies only slightly from those of compounds of a previously known class of compounds (new analogues of fentanyl are an example); through separation, MagLev enables the molecular characterization of those compounds by other techniques. MagLev could aid in the detection of new designer drugs, unconventional mixtures of drugs, fentanyl-laced drugs of inconsistent and unexpectedly high concentration, and harmful adulterants on the illegal market. Circumventing detection by MagLev would require additional and unfamiliar efforts on the part of providers of street drugs. MagLev enables the characterization of dilute compounds in mixtures of powders using techniques that would otherwise not be able to identify the molecular structure of dilute compounds in mixtures of powders.

Note: The views and opinions of authors expressed herein do not necessarily reflect those of the DEA.

Acknowledgements

This work was funded by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering under award no. ER45862. Specifically, the DoE award funded the salary of C.K.A, D.J.P, and S.G. and the cost of materials. A.N acknowledges salary support from DARPA award no. W911NF-18-2-0030 and M.J.F. acknowledges salary support from the Simons Foundation.

Conflict of interest

The authors declare no conflict of interest.

Keywords: chelates · density-based separation · illicit drugs · IR spectroscopy · magneto-Archimedes levitation

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 874–881
Angew. Chem. **2020**, *132*, 884–891

- [1] a) Q.-H. Gao, W.-M. Zhang, H.-X. Zou, W.-B. Li, H. Yan, Z.-K. Peng, G. Meng, *Mater. Horiz.* **2019**, *287*, 64–70; b) S. Ge, A. Nemiroski, K. A. Mirica, C. R. Mace, J. W. Hennek, A. A. Kumar, G. M. Whitesides, *Angew. Chem. Int. Ed.* **2019**, <https://doi.org/10.1002/anie.201903391>; *Angew. Chem.* **2019**, <https://doi.org/10.1002/ange.201903391>; c) E. Turker, A. Arslan-Yildiz, *ACS Biomater. Sci. Eng.* **2018**, *4*, 787–799; d) S. Yaman, M. Anil-Inevi, E. Ozcivici, H. C. Tekin, *Front. Bioeng. Biotechnol.* **2018**, *6*, 192; e) W. Zhao, R. Cheng, J. R. Miller, L. Mao, *Adv. Funct. Mater.* **2016**, *26*, 3916–3932.
- [2] a) European Monitoring Centre for Drugs and Drug Addiction, 10.2810/800331 http://www.emcdda.europa.eu/publications/edr/trends-developments/2018_en, **2018**; b) U.S. Department of Justice, Drug Enforcement Administration, <https://www.dea.gov/sites/default/files/2018-2011/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf>, **2018**; c) U.S. Department of Health and Human Services, Center for Disease Control and Prevention, <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf>, **2018**.
- [3] S. Ge, S. N. Semenov, A. A. Nagarkar, J. Milette, D. C. Christodouleas, L. Yuan, G. M. Whitesides, *J. Am. Chem. Soc.* **2017**, *139*, 18688–18697.
- [4] H. Akil, S. Archer, A. Beaumont, M. Blum, D. Bronstein, S. Childers, A. Corbett, B. Cox, V. Dauge, R. Day, *Opioids I (Handbook of Experimental Pharmacology)*, Springer Science & Business Media, Cham, **2012**, pp. 3–9.
- [5] M. J. Christie, M. M. Morgan in *Encyclopedia of Psychopharmacology* (Ed.: I. P. Stolerman), Springer Berlin Heidelberg, Berlin, **2010**, pp. 936.
- [6] a) G. Curtis, G. Johnson, P. Clark, R. Taylor, J. Brown, R. O'Callaghan, M. Shi, P. Lacouture, *Eur. J. Clin. Pharmacol.* **1999**, *55*, 425–429; b) A. V. George, J. J. Lu, M. V. Pisano, J. Metz, T. B. Erickson, *Am. J. Emerg. Med.* **2010**, *28*, 530–532; c) H. Hedegaard, M. Warner, A. M. Miniño, U. S. Department of Health and Human Services—Center for Disease Control and Prevention, **2017**.
- [7] P. Armenian, K. T. Vo, J. Barr-Walker, K. L. Lynch, *Neuropharmacology* **2018**, *134*, 121–132.
- [8] D. Ciccarone, *Int. J. Drug Policy* **2017**, *46*, 107–111.
- [9] C. Cole, L. Jones, J. McVeigh, A. Kicman, Q. Syed, M. A. Bellis, Centre for Public Health, Liverpool John Moores University, <http://www.cph.org.uk/wp-content/uploads/2012/08/cut-a-guide-to-the-adulterants-bulking-agents-and-other-contaminants-found-in-illicit-drugs.pdf>, **2010**.
- [10] Scientific Working Group for the Analysis of Seized Drugs, http://www.swgdrug.org/Documents/SD-7_FINAL_ForPostingRev_101719.pdf, **2018**.
- [11] J. Ash, L. Hickey, J. Goodpaster, *Forensic Chem.* **2018**, *10*, 37–47.
- [12] R. Gehl, D. Plecas, BCcampus, Justice Institute of British Columbia, <http://uilis.unsyiah.ac.id/oer/files/original/93e658ee61ec01d69c97becccd1221c3.pdf>, **2017**, 137.
- [13] E. Hiolski, *C&EN*, November 20, **2017**, *45*, 37–39.
- [14] a) A. Amlani, G. McKee, N. Khamis, G. Raghukumar, E. Tsang, J. A. Buxton, *Harm Reduct. J.* **2015**, *12*, 54; b) W. Ruangyuttikarn, M. Y. Law, D. E. Rollins, D. E. Moody, *J. Anal. Toxicol.* **1990**, *14*, 160–164; c) G. Wang, K. Huynh, R. Barhate, W. Rodrigues, C. Moore, C. Coulter, M. Vincent, J. Soares, *Forensic Sci. Int.* **2011**, *206*, 127–131.
- [15] M. Philp, S. Fu, *Drug Test. Anal.* **2018**, *10*, 95–108.
- [16] U.S. Department of Justice, Drug Enforcement Administration, <https://www.dea.gov/press-releases/2016/06/10/dea-warning-police-and-public-fentanyl-exposure-kills>, June 10, **2016**.
- [17] a) T. M. Brunt, C. Nagy, A. Bücheli, D. Martins, M. Ugarte, C. Beduwe, M. Ventura Vilamala, *Drug Test. Anal.* **2017**, *9*, 188–

- 198; b) L. Harper, J. Powell, E. M. Pijl, *Harm Reduct. J.* **2017**, *14*, 52.
- [18] a) M. B. Atkinson, D. K. Bwambok, J. Chen, P. D. Chopade, M. M. Thuo, C. R. Mace, K. A. Mirica, A. A. Kumar, A. S. Myerson, G. M. Whitesides, *Angew. Chem. Int. Ed.* **2013**, *52*, 10208–10211; *Angew. Chem.* **2013**, *125*, 10398–10401; b) K. A. Mirica, S. T. Phillips, C. R. Mace, G. M. Whitesides, *J. Agric. Food Chem.* **2010**, *58*, 6565–6569; c) K. A. Mirica, S. S. Shevkoplyas, S. T. Phillips, M. Gupta, G. M. Whitesides, *J. Am. Chem. Soc.* **2009**, *131*, 10049–10058; d) J. Xie, C. Zhang, F. Gu, Y. Wang, J. Fu, P. Zhao, *Sens. Actuators B* **2019**, *295*, 204–214; e) C. Zhang, P. Zhao, F. Gu, J. Xie, N. Xia, Y. He, J. Fu, *Anal. Chem.* **2018**, *90*, 9226–9233.
- [19] C. L. Duvauchelle, T. Sapoznik, C. Kornetsky, *Pharmacol. Biochem. Behav.* **1998**, *61*, 297–302.
- [20] a) R. M. Burks, S. E. Pacquette, M. A. Guericke, M. V. Wilson, D. J. Symonsbergen, K. A. Lucas, A. E. Holmes, *J. Forensic Sci.* **2010**, *55*, 723–727; b) K. M. Elkins, A. C. Weghorst, A. A. Quinn, S. Acharya, *Drug Test. Anal.* **2017**, *9*, 306–310.
- [21] M. P. Elie, L. E. Elie, *Encyclopedia of Analytical Chemistry: Applications, Theory and Instrumentation*, Wiley, Hoboken, **2006**.
- [22] a) A. Barfidokht, R. K. Mishra, R. Seenivasan, S. Liu, L. J. Hubble, J. Wang, D. A. Hall, *Sens. Actuators B* **2019**, *296*, 126422; b) S. A. Goodchild, L. J. Hubble, R. K. Mishra, Z. Li, K. Y. Goud, A. Barfidokht, R. Shah, K. S. Bagot, A. J. McIntosh, J. Wang, *Anal. Chem.* **2019**, *91*, 3747–3753.
- [23] J. Moros, N. Galipienso, R. Vilches, S. Garrigues, M. de la Guardia, *Anal. Chem.* **2008**, *80*, 7257–7265.
- [24] A. Haddad, M. A. Comanescu, O. Green, T. A. Kubic, J. R. Lombardi, *Anal. Chem.* **2018**, *90*, 12678–12685.
- [25] C. Spicher, T. Yeatman, I. Alford, L. Waugh, Marshall University, Marshall University Forensic Science Center, https://www.marshall.edu/forensics/files/SpicherCristina_FINAL-Research-Paper_8_3_-2016.pdf, **2016**.
- [26] CBRNE Tech Index, <http://www.cbrnetechindex.com/Print/3561/thermo-fisher-scientific-inc/trudefender-ftxftxi>, July 10, **2019**.
- [27] U.S. Department of Homeland Security, https://www.dhs.gov/sites/default/files/publications/Portable-Infrared-Spectroscopy-Chemical-Detectors-ASR_0616-508.pdf, **2016**.
- [28] H. R. Kranzler, J. Stone, L. McLaughlin, *Drug Alcohol Depend.* **1995**, *40*, 55–62.
- [29] W. R. de Araujo, T. M. Cardoso, R. G. da Rocha, M. H. Santana, R. A. Munoz, E. M. Richter, T. R. Paixao, W. K. Coltro, *Anal. Chim. Acta* **2018**, *1034*, 1–21.
- [30] a) C. Hodges, P. Hendra, H. Willis, T. Farley, *J. Raman Spectrosc.* **1989**, *20*, 745–749; b) F. W. Langkilde, J. Sjöblom, L. Tekenbergs-Hjelte, J. Mraak, *J. Pharm. Biomed. Anal.* **1997**, *15*, 687–696.
- [31] a) Personal Communication: J. S. Bozenko, Jr., U. S. Department of Justice, Drug Enforcement Administration, January 18, **2019**; b) A. Jenkins, R. Keenan, J. Kivett, K. Demuth, A. Neu, S. Heishman, J. Henningfield, E. Cone, *NIDA Res. Monogr.* **1994**, *141*, 401–401.
- [32] E. Gogolashvili, N. Dzubenko, N. Kuz'mina, B. Y. Margulis, L. Martynenko, *Magn. Reson. Imaging* **1994**, *12*, 299–300.
- [33] U. S. Department of Justice, Drug Enforcement Administration, <https://www.justice.gov/archive/ndic/pubs1/1837/1837t.htm>, **2002**.
- [34] M. Dušek, G. Chapuis, M. Meyer, V. Petricek, *Acta Crystallogr. Sect. B* **2003**, *59*, 337–352.
- [35] J. W. Gruner, *Z. Kristallogr. - Cryst. Mater.* **1934**, *88*, 412–419.
- [36] A. Nemiroski, S. Soh, S. W. Kwok, H.-D. Yu, G. M. Whitesides, *J. Am. Chem. Soc.* **2016**, *138*, 1252–1257.
- [37] C. Coulson, J. P. Caulkins, *Addiction* **2012**, *107*, 766–773.

Manuscript received: August 9, 2019

Accepted manuscript online: November 12, 2019

Version of record online: December 5, 2019