Disintegration Fingerprinting: A low-cost and easy-to-use tool for identifying substandard and falsified medicines

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Abstract

There is an urgent need for low-cost and simple-to-use tools for identifying substandard and falsified medicines. In this work we demonstrate "Disintegration Fingerprinting" (DF), a technique that identifies pills, tablets, caplets, and other solid-dosage drugs based on how the drug disintegrates and dissolves in liquid. The DF hardware consists of a water-filled transparent plastic cup atop a conventional magnetic stirrer. An inexpensive sensor mounted on the outside of the cup shines infrared light into the cup and measures the amount of light that is reflected back to the sensor. When a pill is added to the stirred water, the pill begins to disintegrate into particles that swirl around inside the cup. Whenever one of these particles passes near the infrared sensor, the particle reflects additional light back to the sensor and creates a millisecond-duration peak in a plot of sensor output vs. time. The number of particles in the water changes over time as the particles continue to disintegrate and (in some cases) eventually dissolve away. By plotting the number of particles detected vs. time, we create a Disintegration Fingerprint that can be used to identify the drug product. In a proof-of-concept study, we used DF to analyze 96 pills from 32 different drug products (including antibiotics, opioid and non-opioid analgesics, antidepressants, anti-inflammatories, antiemetics, antihistamines, decongestants, muscle relaxants, expectorants, sleep aids, cold medicines, antacids, hormonal birth control, and dietary supplements, as well as a simulated falsified drug product). We found that DF correctly identified 90% of these pills, and the technique can even distinguish name-brand and generic versions of the same drug. By providing a fast (60-minute), inexpensive ($33 USD), and easy-to-use tool for identifying substandard and falsified medicines, Disintegration Fingerprinting can play an important role in the fight against fake drugs.

Introduction

The World Health Organization (WHO) estimates that 1 in 10 medical products in low- and middle-income countries is substandard or falsified [1], meaning that the products fail to meet either their quality standards or their specifications, or both. Substandard or falsified (SF) medications often lack active pharmaceutical ingredients or contain

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incorrect dosages, making them ineffective or harmful. The global impact of SF medicines is enormous. An estimated 122,000 deaths of children under five years of age were linked to poor-quality antimalarial drugs in 2013 [2]. In low- and middle-income countries (LMICs), 19.1% of antimalarials and 12.4% of antibiotics were found to be substandard or falsified [3], and up to 30% of medicines in parts of Africa, Asia, and Latin America are counterfeit [4]. SF medicines also have a significant economic impact, with an estimated $30 billion USD spent on SF medicines in LMICs annually [1].

Tools for identifying SF medicines can play a crucial role in combating this problem. Some of these tools perform *chemical* analyses to detect the presence or absence of active ingredients. For example, techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry (MS) are gold standards for identifying a wide variety of SF medicines [5] . However, tools like HPLC and MS require expensive equipment and specialized operator training; this limits their accessibility in resource-constrained settings [4]. Low-cost techniques for detecting active ingredients have also been developed. For example, paper analytical devices (PADs) [6] and microfluidic paper-based assays (μPADs) [7] use chromatography and color changes to detect active ingredients, the “PharmaChk” instrument uses aptamers to identify active ingredients [8,9], and the “GPHF-Minilab” kit uses thin-layer chromatography to detect 125 different active ingredients [10]. Tests like these are relatively low-cost and easy-to-use, but they require a supply of consumables (disposable devices, reagents, reference standards, etc.), are tailored for targeting specific chemical compounds, and may not be applicable to all active ingredients.

Other tools perform *physical* analyses to identify SF medicines. These techniques do not directly detect the active ingredient, but they have the advantage of being applicable to virtually all medicines and can be low-cost as well. The most basic form of physical analysis is visual inspection: examining a tablet’s markings, color, surface finish, packaging, and so on. WHO’s “Tool for Visual Inspection of Medicines” is a checklist that guides the user through a 35-step qualitative visual inspection process [11]. For more *quantitative* physical data, the GPHF-Minilab includes calipers and a digital balance for measuring pill size and mass [10], handheld glossmeters can be used to measure pill surface roughness [12], and smartphones can be used to detect inconsistencies indicative of poor manufacturing or deliberate obfuscation [13].

Physical measurements of how a pill disintegrates and dissolves in liquid are particularly interesting because they can be influenced by both the chemical composition of the pill (for example, two pills with different ingredients may dissolve at different speeds, or disintegrate into different-sized particles) and the process used to manufacture the pill (for example, two pills manufactured on different pill presses may disintegrate at different rates). In perhaps the simplest method of this type, a pill is placed into a cup filled with water and a stopwatch is used to record how much time it takes for the pill to disintegrate. This method is included in the GPHF-MiniLab [10], and while it is extremely simple and low-cost, it provides only a single number (a disintegration/dissolution time) and thus has limited ability to distinguish different drug products. Other techniques seek to extract richer data from the disintegration and dissolution process. For example, the dissolution apparatuses described by the US Pharmacopeia are routinely used to measure the release of active ingredients over time as a pill disintegrates and dissolves [14]; a plot of the amount of active ingredient released vs. time could be used to identify a drug product. Other techniques use sound recordings [15] and imaging along with machine learning [16] to monitor the dissolution process. However, while methods like these produce data-rich “fingerprints” from the pill disintegration/dissolution process, the cost of the required hardware makes them less suitable for use in resource-limited settings.

In this work we introduce “Disintegration Fingerprinting” (DF), a low-cost and user-friendly technique for generating unique “fingerprints” based on how a pill disintegrates and dissolves. DF counts the number of drug particles present in solution over time as a drug product disintegrates and dissolves. Instead of using costlier conventional approaches like Coulter counting or dynamic light scattering to count particles, our prototype DF instrument uses a $3.50 USD light sensor originally marketed for use in line-following toy robots. As a typical pill dissolves, the number of particles detected by our sensor initially rises (as the pill disintegrates into particles). Depending on the pill, the particle count may continue to rise (if the particles fragment into smaller particles), or drop (if the particles dissolve away), or remain unchanged (if the particles are insoluble). We call these plots of particle count versus time “disintegration fingerprints” because their shapes vary significantly across different drug products. Consequently, Disintegration Fingerprinting can be used to determine whether two pills are likely the same (if they have similar DFs) or are definitely different (if they have significantly different DFs). Moreover, by constructing a library of DFs for different drug products, Disintegration Fingerprinting could be used to identify a pill (and flag suspect pills for additional scrutiny) in customs offices, clinics, pharmacies, and other settings.

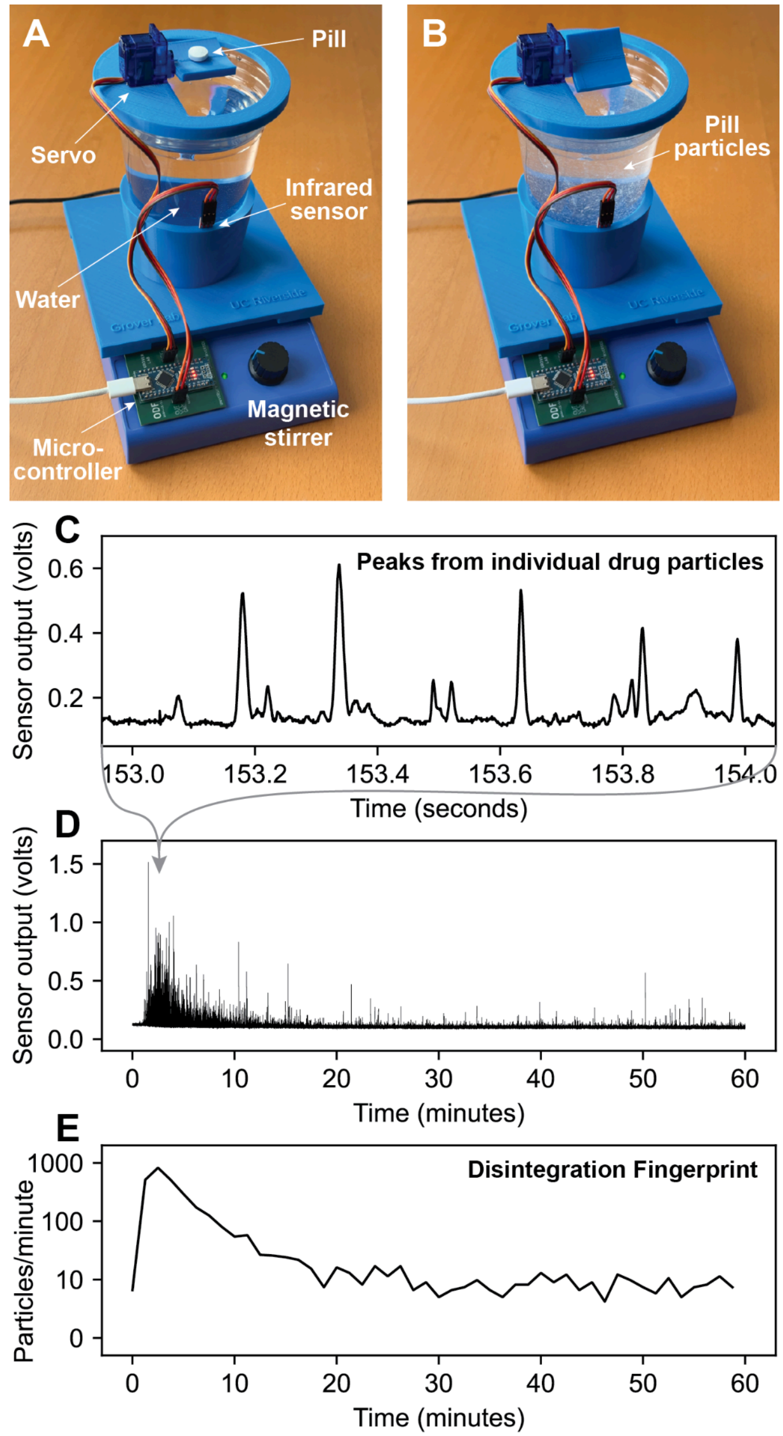


Figure 1: Our prototype Disintegration Fingerprinting apparatus. (**A**) A servo drops a single pill into a water-filled cup atop a magnetic stirrer. The pill begins to disintegrate into particles (**B**), and an infrared optical sensor on the side of the cup detects the light reflected by individual particles as they pass the sensor (**C**). As the particles disintegrate and dissolve further, the number of particles detected changes (**D**). A plot of peak count vs. time (**E**) serves as a "Disintegration Fingerprint" for this pill.

Results

The hardware needed for Disintegration Fingerprinting can vary depending on a user's needs and available resources. At minimum, the technique requires a stirred water-filled vessel to contain the disintegrating medication, a sensor for monitoring the pill disintegration/dissolution process, and electronic hardware for recording the sensor output and calculating the DF. Our prototype DF instrument shown in Figure 1A uses a clear plastic cup, a low-cost magnetic stirrer, an infrared light source/detector, and an Arduino-style microcontroller; these components cost a total of $33 USD. For enhanced convenience and repeatability, the instrument in Figure 1A also includes a servo (to automatically drop a pill into the water at the correct time), a custom printed circuit board (to facilitate assembling the electronics), and custom 3D-printed fixtures (to hold all components in place). These optional components increase the cost of the system to about $42 USD. Details about the instrument design are available in *Materials and Methods*.

To obtain a Disintegration Fingerprint for a pill, the cup is filled with tap water, the stirrer is started, and the pill is placed on the servo platform (Figure 1A). Custom Python software running on a computer connected to the microcontroller records 5 minutes of baseline data from the sensor, then the servo automatically adds the pill to the stirred water (Figure 1B). The software continues to record data from the sensor for an additional 60 minutes. The pill disintegrates into particles, and whenever one of these particles passes near the infrared sensor, the particle reflects some infrared light back into the sensor; this causes a momentary increase in the sensor signal, which results in a peak in the plot of sensor signal vs. time (Figure 1C). For most samples, the number of particles detected in the water varies over the 60-minute run: some samples display more peaks over time (as large particles disintegrate into larger numbers of smaller particles) and some samples have fewer peaks over time (as particles dissolve away and are no longer detected by the sensor). The particular pill analyzed in Figure 1D (an ibuprofen caplet) remains intact for about 1 minute after being added to water, it then disintegrates into a large number of particles by the 3-minute mark, then the number of particles detected slowly drops over the next 20 minutes as the particles dissolve away, but some insoluble particles remain even at the 60-minute mark. By plotting the number of particles detected per minute, we create this pill's Disintegration Fingerprint (DF) shown in Figure 1E. Since the number of particles detected can vary by several orders of magnitude over time for a given pill, we plot DFs using a logarithmic axis for particle count.

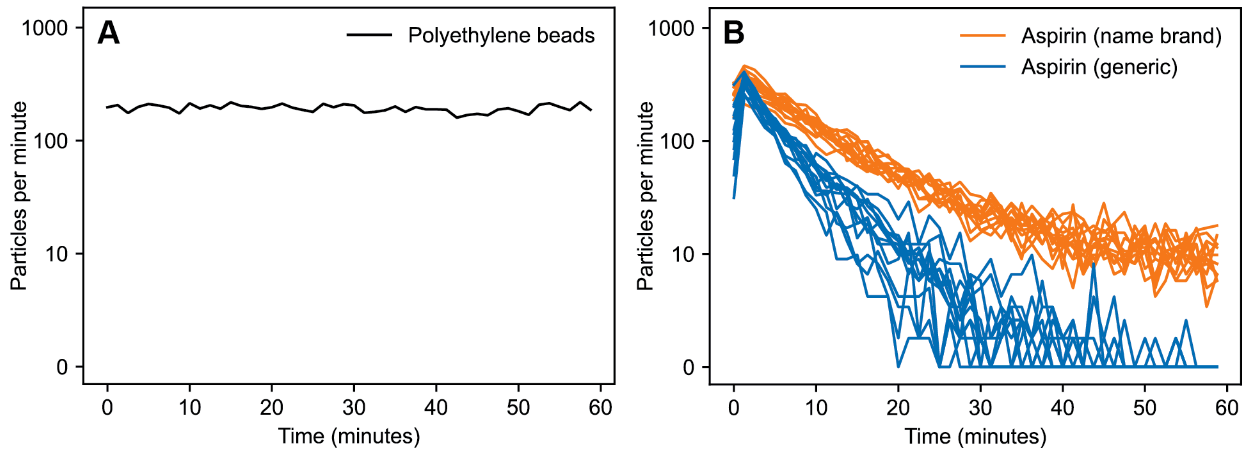


Figure 2: (A) The Disintegration Fingerprint (DF) for a sample of polyethylene beads in water is a flat line, indicating that the number of beads is not changing over time (as expected for insoluble polyethylene). In contrast, the DFs for 26 aspirin pills **(B)** exhibit significant change over time as particles disintegrate and dissolve. Even though the 13 pills of name-brand aspirin (orange) and 13 pills of generic aspirin (blue) have the same dose of the same active ingredient and similar inactive ingredients, the two products are clearly distinguishable by their DFs.

Before using DF to analyze drug samples, we wanted to first confirm that changes in a DF over time really are caused by changes in the number of particles as a drug disintegrates and dissolves. To verify this, we analyzed particle samples that we know do *not* change over time. For example, Figure 2A shows the DF for a sample of 425-500 µm diameter polyethylene beads in water. Since these beads remain intact and polyethylene is not soluble in water, the number of beads detected should remain constant over time. As expected, the DF for this sample is a flat line. This proves that changes in a DF over time are indeed caused by changes in the number of particles over time, and if these changes in particle count are reproducible for a given drug product, then our technique can be used to "fingerprint" drugs based on their disintegration and dissolution behavior.

Any technique for fingerprinting pills should satisfy two criteria: different types of pills should yield different fingerprints, and different pills of the same type should yield similar fingerprints. To determine if disintegration fingerprinting satisfies these criteria, we first used the technique to analyze a large number of pills of two different types. We chose aspirin for this testing because it is one of the most widely used drugs worldwide (with tens of billions of aspirin pills consumed every year) and it is a known target for counterfeiters (e.g., [17]). We analyzed two different aspirin products: a name-brand (Bayer; Whippany, NJ), and a generic (Rite Aid; Philadelphia, PA). Both products have the same amount of active ingredient (325 mg acetylsalicylic acid) and only minor differences in their inactive ingredients (see Table 1 for details), but since they are different products manufactured at different facilities, they should ideally have different Disintegration Fingerprints.

Figure 2B shows Disintegration Fingerprints for 26 aspirin pills, 13 from a bottle of the name-brand product (orange) and 13 from a bottle of the generic product (blue). The different types of pills are easily distinguished by their DFs: the particle count is consistently higher for the name-brand aspirin with particles still detectable at the 60-minute mark, while the particle count for the generic drops more rapidly and no particles are detectable by the 60-minute mark. To quantify our ability to correctly identify these two pill types based on their DFs, for each DF in Figure 2B we calculated the sum of the absolute value of the difference between that DF and each of the other 25 DFs. This resulted in a set of 25 “difference scores” for each pill. We then found the pairing that had the lowest difference score for each pill and determined whether the pills in that pairing were the same type (a successful identification) or different (an unsuccessful identification). In this manner, we found that 100% of these 26 pills were correctly identified based on their Disintegration Fingerprints.

Next, we wanted to test Disintegration Fingerprinting with a wider variety of drug types. We used DF to analyze 32 different types of drugs from a variety of different categories, including antibiotics, opioid and non-opioid analgesics, antidepressants, anti-inflammatories, antiemetics, antihistamines, decongestants, muscle relaxants, expectorants, sleep aids, cold medicines, antacids, hormonal birth control, and dietary supplements. These pills (shown in Table 1) represent an assortment of different sizes and colors, and they include both conventional and extended-release formulations, as well as name-brand and generic manufacturers. Our drug library also included simulated falsified pills that we produced by using a pill press to form powdered milk into tablets.

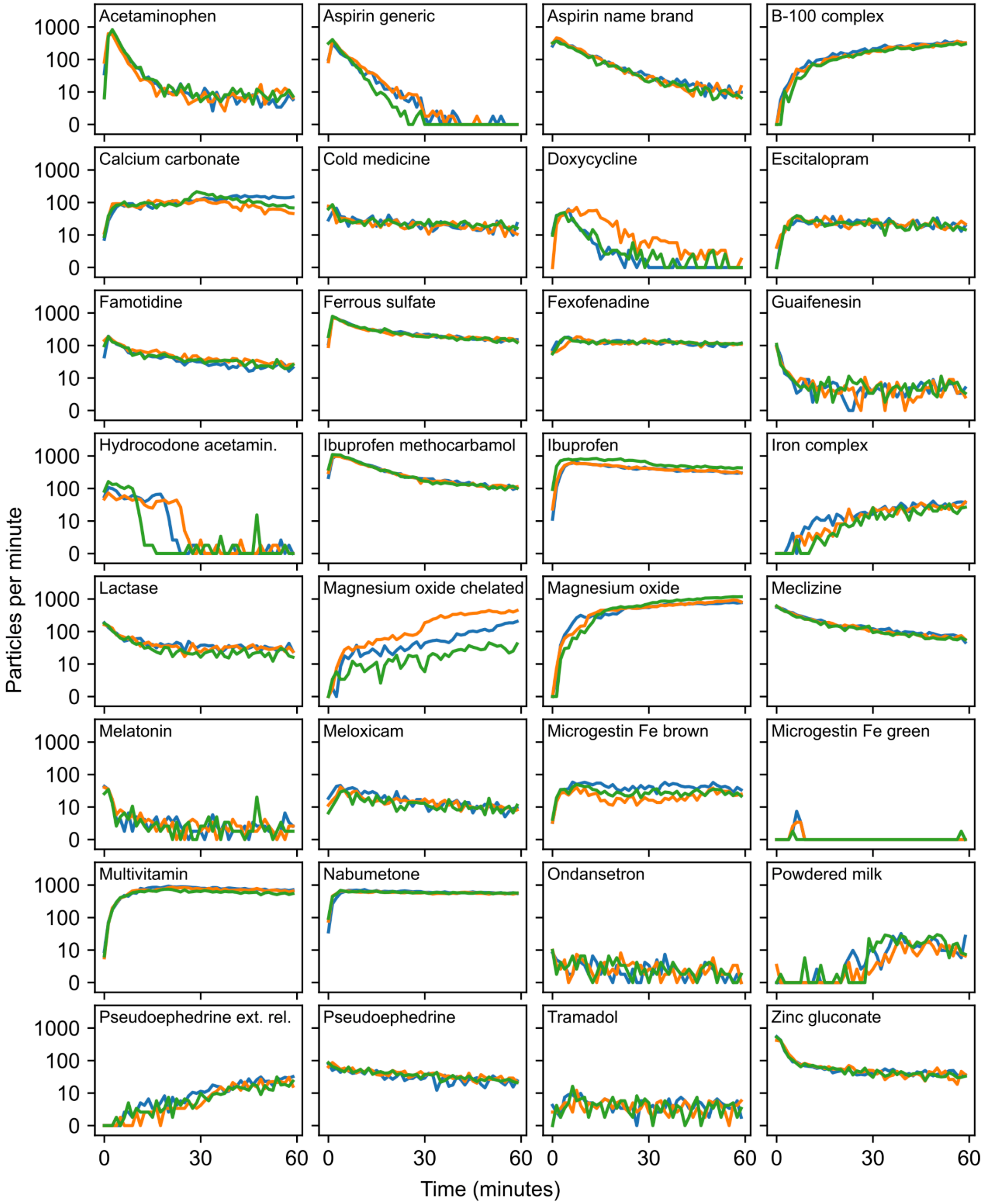


Figure 3: Disintegration Fingerprints for three pills (orange, blue, and green) of each of 32 different drug products.

The results from using DF to analyze our drug library are shown in Figure 3. Each of the 32 plots shows three Disintegration Fingerprints from analyzing three pills of the type shown, for a total of 96 different DFs. Inspecting these plots reveals the striking diversity of the DFs for different drug types, as well as the relative similarity of the three DFs within each drug type. We can also make some qualitative observations about some of the DFs. Some drugs quickly generate a large number of particles, then the particle count drops as the particles dissolve away; examples of this include acetaminophen, name-brand and generic aspirin, doxycycline, guaifenesin, and hydrocodone acetaminophen. Other drugs continue to form more particles throughout the entire 60-minute run; these include the B-100 complex, iron complex, chelated and plain magnesium oxide, and pseudoephedrine extended release. The only type of drug in our library that generated very few detectable particles (and therefore yielded blank DFs) was the Microgestin Fe green pill; this hormone-containing birth control pill is easily distinguished from the placebo Microgestin Fe brown pills in the same package based on their DFs. Finally, to facilitate qualitative comparisons between DFs of the different drug types, we calculated the average DF for each drug type and plotted the 32 results together on the same axes in Figure 4. The striking diversity of the DFs in Figure 4 supports our claim that different drug products are likely to have different DFs.

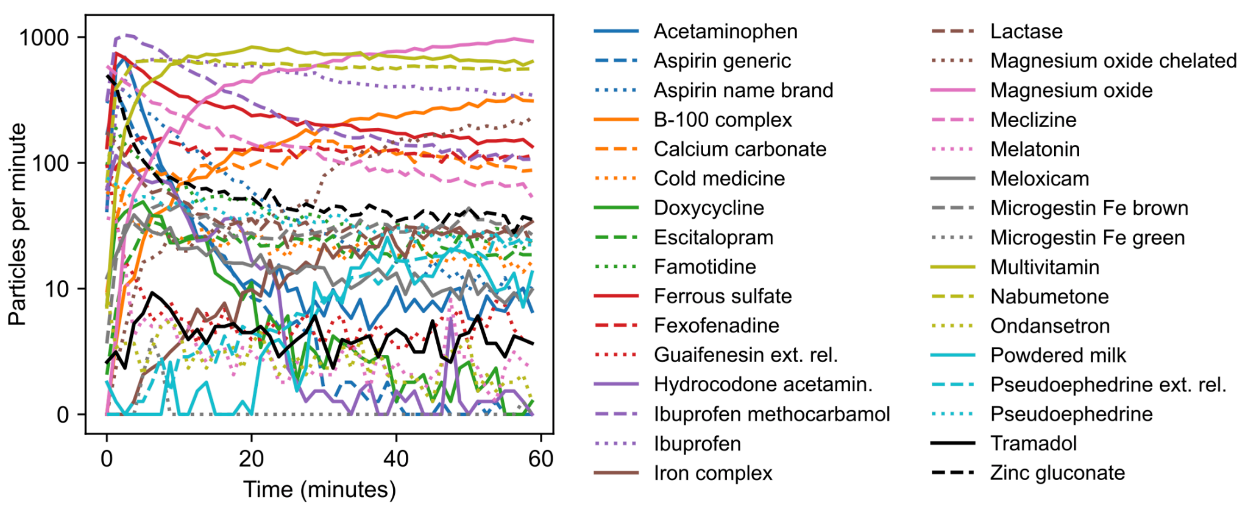


Figure 4: Averaged Disintegration Fingerprints for each of the 32 drug products in Figure 3, showing the large variety of DFs across different drug products.

To quantify our ability to identify a drug product using DF, we calculated the absolute value of the difference between all pairs of DFs in Figure 3. This resulted in a set of 95 “difference scores” for each pill. We ranked these scores to find the closest DF match for each of the 96 pills, then determined whether that match was with one of the two other pills of the same type (a successful identification) or with one of the 93 pills of different types (an unsuccessful identification). Using this approach, we found that

Disintegration Fingerprinting correctly identified 86 of the 96 pills, a success rate of 90%. Of the 10 pills that were misidentified, seven of the pills were the only pills of their type that were misidentified (meaning that the other two pills of that type were correctly identified). The remaining three misidentified pills were all of the same type, magnesium oxide chelated. In other words, for the 32 different drug products in Figure 3, 31 of them (97%) had at least two of the three pills successfully identified using DF.

While collecting Disintegration Fingerprints for the 32 different drug products in Figures 3 and 4, we observed that four of the products did not fully disintegrate by the end of the 60-minute run. Not surprisingly, all four of these slow-disintegrating products were marketed by the manufacturers as having a “prolonged release,” “time release,” or “extended release” of active ingredients. To see if Disintegration Fingerprinting can offer insights into the behavior of extended-release drug formulations, we obtained 10-hour-long Disintegration Fingerprints for three pills of each of these four drug products. The results in Figure 5 show that the disintegration behavior of these prolonged-release formulations is still changing even hours after being placed in water. One of the B-100 complex pills (blue trace) matched most closely with one of the iron complex pills. The other 11 pills matched correctly with other pills of the same type—a success rate of 92%, similar to what we obtained for the 60-minute runs in Figure 3. Therefore, significantly increasing the duration of the DF does not seem to have a significant effect on the technique’s ability to identify drug products, at least for the products studied here. However, the long-duration DFs in Figure 5 do show that Disintegration Fingerprinting can provide insights into the behavior of controlled-release pharmaceuticals. For example, the guaifenesin pills show two distinct peaks in their DFs, an early release of particles in the first few minutes after the pill is added to water (also visible in Figure 3), and a later secondary release of particles that peaks around the 3-hour mark. Information like this could be useful to pharmaceutical companies’ formulation and quality assurance labs.

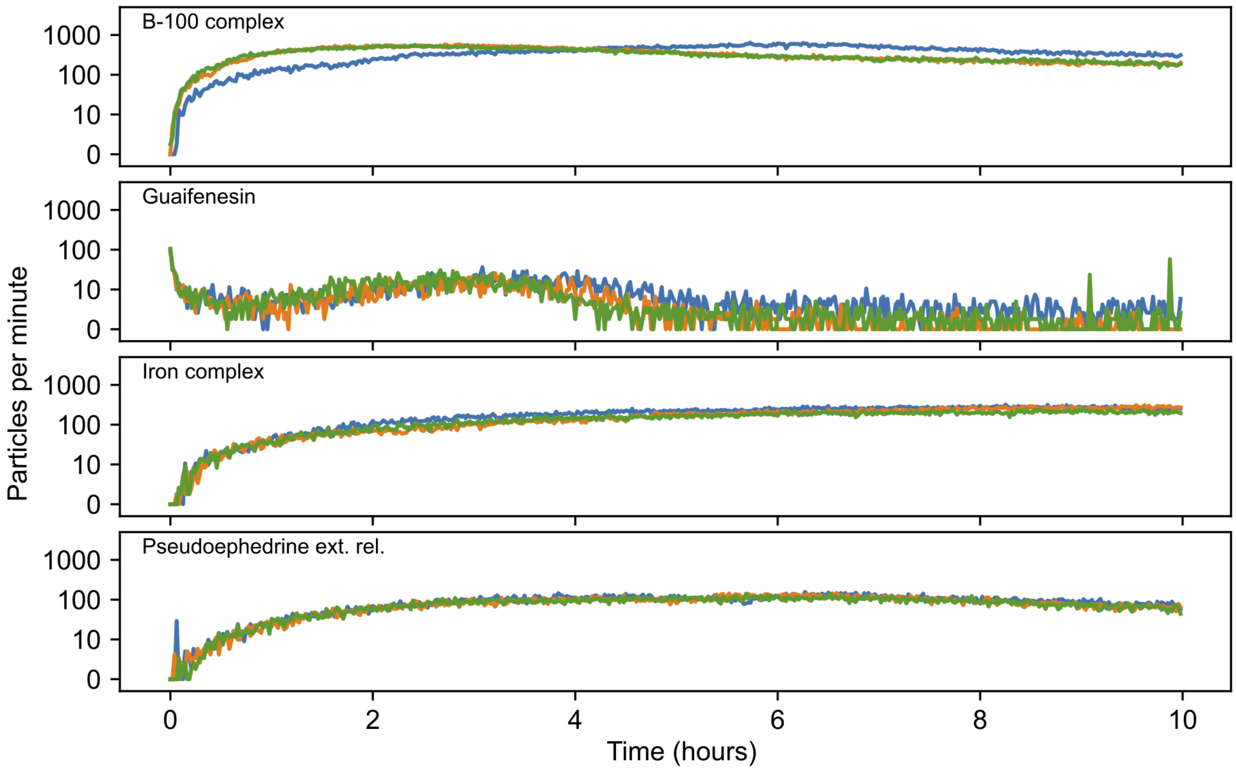


Figure 5: Ten-hour-long Disintegration Fingerprints for three pills (orange, blue, and green) of each of four different extended-release drug products.

Conclusions

In this work, we showed that a $42 USD device is capable of correctly identifying 90% of pills in a library of 32 different drug products (and for 97% of the drug products tested, the device successfully identified at least two of the three pills tested). We conclude by reflecting on some of the strengths, weaknesses, and future directions of the Disintegration Fingerprinting technique.

In addition to its low cost, Disintegration Fingerprinting requires no consumables (reagents or single-use devices); this makes the technique particularly suitable for use in settings without reliable supply chains. Additionally, no laboratory-grade purified water is needed, as we performed our analyses using ordinary tap water. DF can be used to fingerprint *any* solid-dosage drug that disintegrates into particles in liquid. Operating our prototype DF instrument requires no specialized training. Setting up an experiment takes only a few seconds, after which the operation of the instrument is completely automated.

The runtime of our prototype DF instrument, currently 60 minutes per sample, makes our instrument slower than many of the existing techniques mentioned earlier.

Obviously, faster is better for many applications, and it may be possible to obtain adequate DFs for some applications in less than 60 minutes. For example, Figure 2B shows that by the 10-minute mark the name-brand and generic aspirin DFs are already clearly distinguishable.

Disintegration Fingerprinting does not provide information about the presence or amount of active ingredients in a drug product. Consequently, DF is best suited for use as a presumptive test for flagging suspect samples for additional confirmatory testing using (much more expensive) tools such as HPLC and MS. Additionally, DF could be very powerful when paired with low-cost techniques that *do* detect active ingredients, such as the aforementioned PADs [6], μPADs [7], and the GPHF MiniLab [10].

For 10% of the pills in our test library, Disintegration Fingerprinting did not successfully identify the pill. How could the technique be improved to reduce this error rate? One relatively simple but potentially powerful modification would be to obtain DFs in additional liquids. For example, many drug products have enteric coatings that keep the pill intact in the acidic contents of the stomach but allow the pill to disintegrate in the more alkaline contents of the intestines. By obtaining DFs for a drug product in two different liquids, one with a pH ~3 and another with pH ~8, we could verify the presence of an enteric coating based on the resulting DFs. Additionally, since the solubility of many substances is influenced by pH, obtaining DFs in different-pH liquids would make the technique even more sensitive to differences in the chemical compositions of different drug products. Likewise, since solubility is also influenced by temperature, two drug products that have indistinguishable DFs at one temperature might be expected to have different DFs at other temperatures. And since different substances also have different solubilities in different solvents, obtaining DFs in additional *non-aqueous* liquids could further enhance the discrimination ability of the technique (for example, since acetylsalicylic acid is more soluble in ethanol than water, one would expect an authentic aspirin would generate particles that dissolve faster in ethanol than in water).

Another likely source of error in our prototype DF instrument concerns our stirrer. The rate at which a solid-dosage drug disintegrates in water is heavily influenced by how much agitation the water is receiving; for this reason, the various USP dissolution apparatuses are engineered to apply a precisely-controlled amount of agitation to pills as they disintegrate. In contrast, the magnetic stirrer used in our prototype DF instrument costs just $24 USD and does not provide fine control; we merely adjusted its speed until the vortex extended 1 to 2 cm below the surface of the water. Magnetic stirrers are known to be sources of inconsistencies: researchers found that chemical reactions can have irreproducible results because of variations in the location of a container atop a stirrer [18]. Therefore, replacing our low-cost magnetic stirrer with a more consistent tool for applying agitation (likely a paddle-based design, like the ones used in some USP dissolution apparatuses [14]) would likely improve the reproducibility of our technique, albeit probably at greater expense.

The algorithms we used in this preliminary demonstration are simplistic and could be outperformed by more sophisticated methods. There is clearly information present in the raw plot of sensor signal vs. time (Figure 1D) that is absent from the plot of peak count vs. time (Figure 1E). Algorithms that compare pills based on their raw plots of sensor signal vs. time could exploit not only differences in peak counts, but also differences in peak heights, peak widths, baselines, and more. Similarly, the algorithm we used to quantify the similarity between two Disintegration Fingerprints—summing the differences between the curves at each point—is very basic. More sophisticated algorithms that are sensitive to differences in curve shapes (and not just arithmetic differences between peak counts) could outperform the approach shown here.

We are hopeful that Disintegration Fingerprinting can join the ranks of other low-cost and user-friendly tools in the fight against substandard and falsified medicines. Our preliminary results here suggest that the technique has potential, but field testing is a necessary next step. To facilitate widespread evaluation and adoption of DF, all of our CAD files and code are open source and freely available for download [19].

Materials and Methods

Hardware

Our prototype Disintegration Fingerprinting instrument (Figure 1) uses an optical sensor marketed for use in line-following robot toys (RedBot line follower sensor QRE1113GR; SparkFun Electronics, Boulder, CO; $4.15 USD). The sensor consists of an LED that emits infrared light (940 nm) placed beside a phototransistor; when an object is placed in front of the sensor, light from the LED is reflected or scattered by the object and detected by the phototransistor. The voltage output of the sensor is measured using an Arduino Nano microcontroller clone.

The optical sensor is held against the side of a disposable transparent PET plastic cup (18 ounces; Solo Cup Company, Lake Forest, IL) with a height of 120 mm, top diameter of 100 mm, and base diameter of 64 mm. The cup is placed on a low-cost magnetic stirrer (INTLLAB, Greenwood, IN; $23.99 USD) and a 25.4 × 8 mm Teflon-coated magnetic stir bar is added.

For convenience and reproducibility, we also designed some optional custom components for the DF instrument. 3D-printed fixtures (shown in blue in Figure 1) hold the cup in place on the stirrer, hold the optical sensor at a fixed location against the side of the cup (3.5 cm from the bottom of the cup), and hold a servo above the cup. The servo (SG90; TowerPro Ltd, Taipei, Taiwan) automatically drops a pill into the cup at the desired time during a run. The 3D-printed fixtures were printed using a low-cost hobbyist-grade 3D printer (Ender 3, Creality, Shenzhen, China). Finally, a custom printed circuit board (shown in green in Figure 1) simplifies the electrical connections between the Arduino Nano clone, the optical sensor, and the pill-dropping servo. CAD files for each of these custom components are available for download [19].

Software

Custom software was used to program the Arduino Nano microcontroller clone; the software relays sensor measurements to the attached computer via USB and operates the pill-dropping servo at the desired time. Additional software (written in Python and running on the attached computer) records the sensor measurements, converts these measurements into Disintegration Fingerprints, performs comparisons between pairs of DFs, and generates the plots shown in the above figures. This software runs on both Windows and MacOS computers and is available for download [19].

Disintegration Fingerprinting algorithms

Our code for converting raw sensor voltage data into Disintegration Fingerprints follows several steps:

1. Very rarely, the computer may record individual voltage measurements from the Arduino Nano that are outside of the range of the microcontroller's analog-to-digital converter (0 to 1023 arbitrary units, corresponding to 0 to 5 volts). This can be caused by electromagnetic interference from *e.g.* a nearby static electricity spark corrupting data on the interface between the microcontroller and the computer. We replaced these corrupted measurements with the previous valid measurement. In the 96-pill dataset analyzed in Figure 3, there are a total of about 8×10^8 individual voltage measurements; only 45 of these measurements had to be replaced due to out-of-dynamic-range values, or about 0.000001% of the measurements.

2. The raw data was inverted (all measurements subtracted from 1023) to make particle peaks point in a positive (upward) direction.

3. Data before the 5-minute mark was discarded (only the data after the pill is added is analyzed).

4. Noise peaks are rare single voltage measurements that are significantly different from their neighboring measurements; they can be caused by spurious electrical signals like a static spark in the vicinity of the instrument or electrical noise created by the servo during motion. These noise peaks are detected using the SciPy [20] function **scipy.signal.find_peaks()** with a threshold of 20 (this identifies individual

measurements that are more than 20 arbitrary units different from their immediately preceding and following measurements). The noise peak values were then removed and replaced by the average of the two neighboring measurements. Out of the approximately 8×10^8 individual voltage measurements in the 96-pill dataset in Figure 3, only 136 measurements had to be replaced due to noise, or about 0.00002% of the measurements.

5. A moving linear regression of the sensor data was calculated to find baseline shifts indicative of bubble formation on the cup wall near the optical sensor. Bubbles are characterized by a slow rise in the baseline signal (as the bubble forms near the sensor) followed by a sudden drop in the baseline signal (as the bubble detaches and leaves the sensor area). To detect these bubble-induced baseline drops, we used a moving window with a width of 50 seconds. If the slope of the data in this moving window is ever less than -0.2 arbitrary units/second, then the run is flagged as containing a bubble and is discarded. In the 96-pill dataset in Figure 3, two of the runs were discarded due to bubble detection (one Microgestin Fe green pill, and one doxycycline pill) and replaced by analyzing another pill of the same type (these were both successful).

6. To locate peaks corresponding to drug particles passing the sensor, the **scipy.signal.find_peaks()** function was used with a prominence threshold of 10.

7. To count drug particle peaks over time, the peak data was partitioned into bins of equal time lengths, then the number of peaks in each bin was divided by the bin duration to obtain the particles-per-second for that bin. The chosen bin duration determines the number of points in the resulting Disintegration Fingerprint; the duration used in this work (75 s) produces a DF with 48 points. Each bin's peak count was increased by 1 (to avoid having values of 0 on a logarithmic plot) and plotted on a logarithmic axis vs. time to create the Disintegration Fingerprints shown in Figures 1 through 5.

To calculate the similarity of two Disintegration Fingerprints, we subtracted the peak counts for each bin on the DFs, calculated the absolute value of this difference, and calculated the sum of the absolute values to create a single number, a difference score. These scores range from the hundreds (for very similar DFs) to the low thousands (for very different DFs).

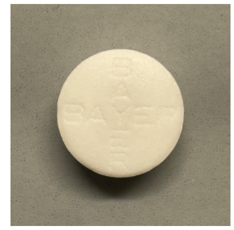
To find matches, we compared each pill's Disintegration Fingerprint to every other pill's DF in a given data set. For example, for the 96-pill dataset in Figure 3, each pill's DF was compared to the other 95 pills (pills were not compared to themselves) and 95 difference scores were calculated. These comparisons were then ranked from lowest difference score (most similar) to highest (least similar). If a pill's closest match was another pill of the same type, then we considered the pill successfully identified.

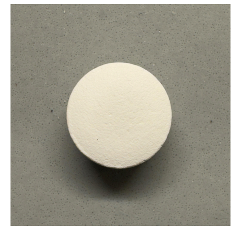
Sample testing

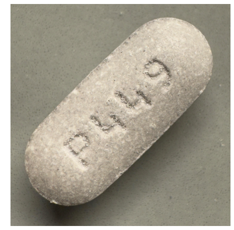
Since purified laboratory water may not be readily available in all locations where Disintegration Fingerprinting might be used, all samples were analyzed in ordinary tap water. The data in Figure 2A was obtained using 50 mg of inert red polyethylene microspheres (425-500 µm diameter, 1.0648 g/mL density; Cospheric, Santa Barbara, CA). Approximately 100 µL of detergent (Palmolive dish soap; Colgate-Palmolive, New York, NY) was added to the water to keep the microspheres from clumping. The 31 drug products tested in Figures 2B and 3–5 were obtained from various locations in the Riverside, CA area; their manufacturers and ingredients are shown in Table 1. The simulated falsified pills tested alongside the authentic drug products in Figure 3 were made by compressing powdered milk (Carnation instant nonfat dry milk, Nestle, Arlington, VA) using a 10-mm-diameter manual pill press (MUHWA Scientific, Shanghai, China).

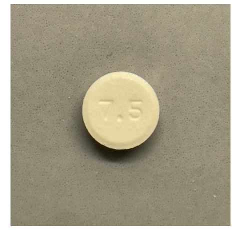
Table 1: Drug products tested using Disintegration Fingerprinting in Figures 3 and 4, and summary of the testing results

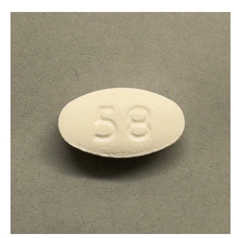
Drug	**Purpose**	**Ingredients**	**Image**
Acetaminophen (Tylenol) McNeil Consumer Healthcare, Fort Washington, PA 3 pills ID'd OK	Non-opioid analgesic	500 mg acetaminophen, carnauba wax, castor oil, corn starch, FD&C red no. 40 aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, powdered cellulose, pregelatinized starch, propylene glycol, shellac, sodium starch glycolate, titanium dioxide	
Aspirin (generic) Rite Aid Corporation, Camp Hill, PA 3 pills ID'd OK	Non-opioid analgesic	325 mg aspirin, corn starch, hypromellose, polyethylene glycol, propylene glycol	

Aspirin (Bayer) Bayer, Leverkusen, Germany 3 pills ID'd OK	Non-opioid analgesic	325 mg aspirin, corn starch, hypromellose, powdered cellulose, triacetin	
B-100 complex Nature Made, West Hills, CA 3 pills ID'd OK	Supplement	Various, cellulose gel, hypromellose, stearic acid, magnesium stearate, silicon dioxide, croscarmellose sodium, polyethylene glycol	
Calcium carbonate Rugby Laboratories, Livonia, MI 3 pills ID'd OK	Antacid	500 mg calcium carbonate, dextrose, flavors, magnesium stearate, maltodextrin, starch, sucralose	
Cold medicine (Sudafed PE Pressure Pain Cold); McNeil Consumer Healthcare, Fort Washington, PA 3 pills ID'd OK	Non-opioid analgesic, decongestant, expectorant, cough suppressant	325 mg acetaminophen, 10 mg dextromethorphan, 100 mg guaifenesin, 5 mg phenylephrine, carnauba wax, croscarmellose sodium, FD&C yellow 5 aluminum lake, FD&C yellow 6 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide	
Doxycycline Avet Pharma, East Brunswick, NJ 2 pills ID'd OK 1 pill ID'd as hydrocodone acetaminophen	Antibiotic	100 mg doxycycline*	
Escitalopram Zhejiang Huahai Pharmaceutical, Zhejiang, China 3 pills ID'd OK	Antidepressant	20 mg escitalopram*	

Famotidine Perrigo, Allegan, MI 3 pills ID'd OK	Antacid	10 mg famotidine, carnauba wax, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, talc, titanium dioxide, triacetin	
Ferrous sulfate Nature Made, West Hills, CA 3 pills ID'd OK	Supplement	325 mg ferrous sulfate, cellulose gel, dibasic calcium phosphate, croscarmellose sodium, hypromellose, color, magnesium stearate, polyethylene glycol, triethyl citrate, polysorbate 80	
Fexofenadine Dr. Reddy's Laboratories, Princeton, NJ 3 pills ID'd OK	Antihistamine	180 mg fexofenadine hydrochloride*	
Guaifenesin extended-release APL Healthcare Limited, Ambatapur, India 3 pills ID'd OK	Expectorant	1200 mg guaifenesin, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch	
Hydrocodone acetaminophen Mallinckrodt Pharmaceuticals, Dublin, Ireland 2 pills ID'd OK 1 pill ID'd as aspirin generic	Opioid and non-opioid analgesic	5 mg hydrocodone, 325 mg acetaminophen*	
Ibuprofen Ascend Laboratories, Bedminster, NJ 2 pills ID'd OK 1 pill ID'd as nabumetone	Anti-inflammatory analgesic	600 mg ibuprofen*	

Ibuprofen and methocarbamol Vita Health Products, Winnipeg, Manitoba, Canada 3 pills ID'd OK	Muscle relaxant and analgesic	200 mg ibuprofen, 500 mg methocarbamol*	
Iron complex Sprouts Farmers Market, Phoenix, AZ 2 pills ID'd OK 1 pill ID'd as cold medicine	Supplement	29 mg iron glycinate, various other nutrients, modified cellulose, calcium stearate, stearic acid, silica, sodium copper chlorophyllin	
Lactase AmerisourceBergen, Conshohocken, PA 3 pills ID'd OK	Supplement	3000 units lactase enzyme, microcrystalline cellulose, mannitol, sodium citrate, sucralose, magnesium stearate	
Magnesium oxide Nature Made, Mission Hills, CA 3 pills ID'd OK	Supplement	250 mg magnesium oxide, cellulose gel, croscarmellose sodium, stearic acid, hypromellose, magnesium stearate, silicon dioxide, color, polyethylene glycol, triethyl citrate, polysorbate 80	
Magnesium oxide chelated Sprouts Farmers Market, Phoenix, AZ 3 pills ID'd as Microgestin Fe brown, B-100 complex, and iron complex	Supplement	250 mg magnesium oxide amino acid chelate, cellulose, dicalcium phosphate, modified cellulose gum, stearic acid, silica, magnesium stearate, glutamic acid, protein hydrolysate, titanium dioxide, glycerin	
Meclizine Rugby Laboratories, Indianapolis, IN 3 pills ID'd OK	Antiemetic	12.5 mg meclizine HCl, croscarmellose sodium, dicalcium phosphate, magnesium stearate, microcrystalline cellulose, silicon dioxide, stearic acid	

Melatonin CVS Pharmacy, Woonsocket, RI 3 pills ID'd OK	Sleep aid	10 mg melatonin, mannitol, crospovidone, stearic acid, natural cherry flavor, beet juice color, malic acid, sucralose, magnesium stearate	
Meloxicam Unichem Pharmaceuticals, East Brunswick, NJ 3 pills ID'd OK	Anti-inflammatory analgesic	7.5 mg meloxicam*	
Microgestin Fe brown Warner Chilcott, Fajardo, Puerto Rico 2 pills ID'd OK 1 pill ID'd as escitalopram	Placebo, supplement	75 mg ferrous fumarate*	
Microgestin Fe green Warner Chilcott, Fajardo, Puerto Rico 3 pills ID'd OK	Hormonal birth control	1.5 mg norethindrone acetate, 30 mcg ethinyl estradiol	
Multivitamin One A Day; Bayer HealthCare, Whippany, NJ 2 pills ID'd OK 1 pill ID'd as nabumetone	Supplement	Various*	
Nabumetone Glenmark Pharmaceuticals, Mumbai, India 3 pills ID'd OK	Anti-inflammatory analgesic	750 mg nabumetone*	

Ondansetron Rising Health, Saddle Brook, NJ 3 pills ID'd OK	Antiemetic	4 mg ondansetron*	
Powdered milk 3 pills ID'd OK	Simulated falsified drug	Powdered milk	
Pseudoephedrine CVS Pharmacy, Woonsocket, RI 3 pills ID'd OK	Decongestant	30 mg pseudoephedrine HCl, croscarmellose sodium, dicalcium phosphate, FD&C red 40 aluminum lake, FD&C yellow 6 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, silica gel, titanium dioxide, triacetin	
Pseudoephedrine extended-release Sudafed sinus congestion 12 hour; McNeil Consumer Healthcare, Fort Washington, PA 3 pills ID'd OK	Decongestant	120 mg pseudoephedrine HCl, carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide	
Tramadol Teva Pharmaceuticals, Parsippany, NJ 2 pills ID'd OK 1 pill ID'd as ondansetron	Opioid analgesic	50 mg tramadol*	
Zinc Nature's Bounty, Bohemia, NY 3 pills ID'd OK	Supplement	50 mg zinc gluconate, cellulose, dicalcium phosphate, <2% of silica, magnesium stearate, stearic acid	

Summary 86 pills ID'd OK 10 pills ID'd wrong			

* Inactive ingredients not available

Supplementary Material

Available for download [19]:

- CAD files for optional custom components (3D printed fixtures and printed circuit board)
- Arduino code for programming Nano microcontroller clone
- Python code for acquiring, comparing, and plotting Disintegration Fingerprints
- Raw data from experiments shown in Figures 2 through 5

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