

Integrated Sensing and Processing - Acoustic Resonance Spectrometry (ISP-ARS) in Differentiating D-Tagatose and Other Toll Manufactured Drugs

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ABSTRACT

Integrated sensing and processing acoustic resonance spectroscopy (ISP-ARS) is a novel approach to acoustic spectroscopy that can be implemented using instruments as simple as an MP3 player. In ISP-ARS, an ISP acoustic excitation waveform is created that comprises only the distinguishing spectral details associated with an analyte. Fourier transform acoustic resonance spectroscopy (FTARS) is used to develop ISP acoustic waveforms employed in differentiating D-tagatose, a new oral drug in phase 3 clinical trials for treatment of type 2 diabetes, from other toll-manufactured drugs. ISP-ARS reduces the time required for processing that is normally observed with full spectrum FTARS. The ISP detector output is a voltage that can be read immediately and corresponds only to the analyte under investigation. ISP acoustic waveforms composed of 10, 100, and 1000 frequencies were used to identify several drugs. The tablets used in this study were aspirin, acetaminophen, D-tagatose, ibuprofen, vitamin B, and vitamin C. It was found that a mixture of as few as ten frequencies with the largest factor loadings were required to properly classify each pill used in this study. Intra-cluster distances were calculated to be less than three multidimensional standard deviations (MSD) for each pill type. The average accuracy of prediction was 98.47, 97.45 and 95.41 percent for the 10, 100 and 1000

frequency component acoustic waveforms respectively.

INTRODUCTION

Each year over 200,000 U.S. citizens die of complications resulting from type II diabetes¹. As a chronic disease, type II diabetes occurs when the body no longer uses insulin effectively. This is compounded by poor insulin production, which leads to high glucose levels in the blood. Hyperglycemia can lead to heart, eye, blood vessel, kidney and nervous disorders and if left unchecked can lead to death. Current statistics suggest that approximately 19 - 20 million Americans have type II diabetes². It is projected that 366 million people worldwide will be afflicted with type II diabetes by the year 2030³. In 2002 it was estimated that in the U.S. alone \$132 billion was spent on treatment of type II diabetes and complications associated with it⁴. D-tagatose (D-tag) is being investigated as a novel treatment for type II diabetes. D-tag is a hexose bulk sweetener with 92% of the sweetness of sucrose, and is naturally occurring in heated dairy products. Although D-tag does not improve insulin production, it has been shown to lower glycemic response as well as induce weight loss in clinical trials through a mechanism of action based on several enzymes in the liver⁵⁻⁶. Experimental drugs like D-tag that are in clinical trials are often produced by contract manufacturers in multiple dosage levels,

and new process analytical techniques must be developed for each new drug to insure identity, concentration and quality.

Many large pharmaceutical manufacturers also contract out their small-scale manufacturing needs as a way of reducing cost or meeting their production deadlines. As a result, a contract manufacturer may make several kinds of pills that are similar in appearance at almost the same time, testing various dosages and placebos for clinical trials. In addition, a contract manufacturer may produce pills for multiple outside firms. One way to reduce the possibility that pills may inadvertently become confused or contaminated is to employ a rapid and nondestructive means of verifying tablet identity. Such systems for identifying contaminated or mislabeled products must be strategically placed to prevent problems with pills before they are shipped. Process analytical technologies (PAT) on the production line should have the ability to work in real-time. Currently there are no fool-proof processes to eliminate mislabeling or contamination, and millions of pills can sometimes be recalled. For example, in November of 2006, 11 million bottles of contaminated acetaminophen were recalled by the Perrigo Company of Allegan, Michigan due to contamination of the tablets with metal wire⁷. The FDA admits that current good manufacturing processes (cGMP) have reached their limits and better risk-based scientific approaches are needed to insure product safety⁸. PATs are designed to prevent large recalls by detecting problems before they occur.

ISP-ARS is fast and non-destructive. Acoustic methods are able to deeply penetrate many types of opaque packaging, in contrast to near-infrared and other optical methods. The ability to penetrate many types of packaging can be a distinct advantage in preparation of clinical trial lots, where drugs and placebos must be blinded from users. As a PAT, a series of ISP-ARS sensors could potentially scan every pill produced by a manufacturer, enabling the removal of only those pills that did not meet quality standards. A dynamic data-driven application system (DDDAS) could control a manufacturer's product line based on measurements from a series of ISP-ARS sensors, adjusting process conditions and ingredients in real time based on actual process measurements⁹⁻¹⁰.

A dynamic data-driven application system (DDDAS) allows for the implementation

of real-time data to model or predict a measurement or event. By incorporating data dynamically rather than statically, the predictions and measurements become more reliable. For example, in weather forecasting, if predictions are made based on static data collected from sparsely distributed sensors, then rapidly changing conditions often make a prediction obsolete shortly after it is made. A more reliable forecasting system continuously incorporates real-time changes from many sensors into its predictions so that the forecast is always built around current conditions. As the conditions change so does the forecast, in real-time. In this way, DDDASs have the ability to guide their measurement processes and focus their resources, such as forecasts guide US Air Force 53rd Weather Reconnaissance Squadron ("Hurricane Hunter") aircraft away from calm seas and into the eyes of hurricanes to concentrate their data collection. The information collected makes possible advance warning of hurricanes and increases the accuracy of hurricane predictions and warnings by as much as 30 percent¹¹.

Creation of the ISP acoustic wave begins with the chemometric analysis of the initial FTAR spectroscopic data. Therefore, FTARS itself makes a prediction about what will work as an ISP acoustic waveform for a given set of samples. This training process can be viewed as a DDDAS when the performance of the ISP waveform is continuously monitored and the ISP waveform is continuously adjusted through retraining. To illustrate, in pharmaceutical production, ISP waveforms are constructed from analysis of the FTARS spectra of active ingredients. As tablets are produced, they can be classified using ISP-ARS. If the sample cannot be identified with the ISP waveform, then FTARS is used again with other reference methods to classify the new sample, recalibrate the ISP waveform, and enable ISP to predict a new unknown (see Fig 1).

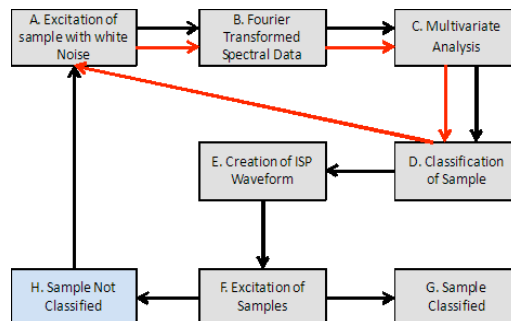


Fig. 1 Block diagram of ISP-ARS process. The red arrows indicate the traditional FTARS cycle. In traditional FTARS, samples are scanned and classified according to their inter-cluster distances found via multivariate analysis (A-D). This process is repeated for each sample scanned. With ISP-ARS, the FTARS data are used to calculate factor loadings and an ISP acoustic waveform is constructed to represent these loadings (E). Once the ISP waveform is constructed, the traditional FTARS operation cycle is not needed. Samples scanned with the ISP waveform are classified according to their detector voltages (F-G). If a sample cannot be classified (H), then FTARS is employed for recalibration and a new ISP acoustic waveform is constructed that includes the new unknown. As samples change the ISP waveform can evolve with the new data.

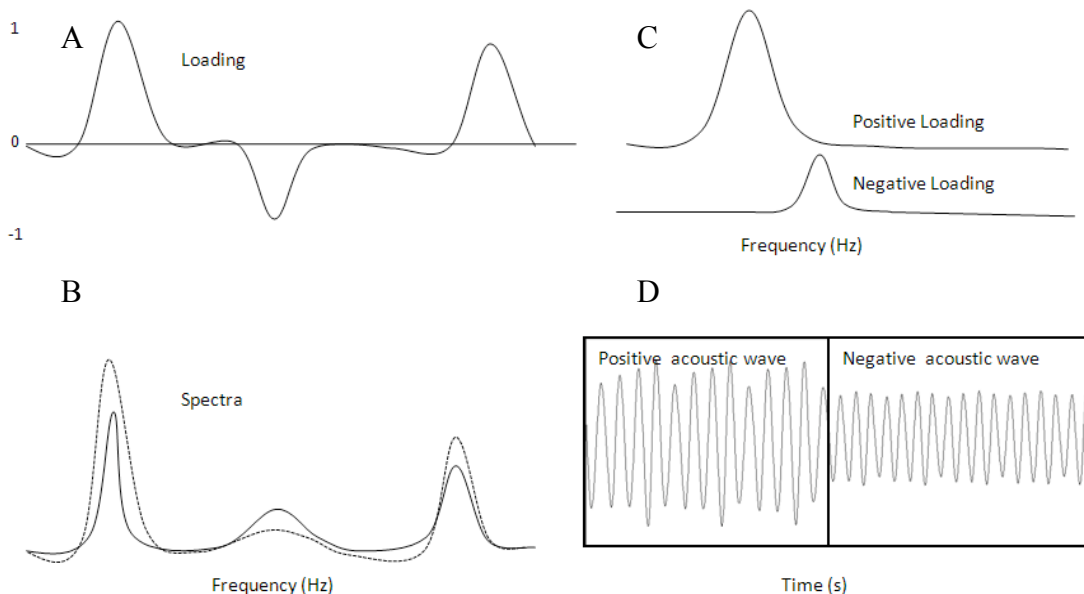
Fourier transform acoustic resonance spectroscopy (FTARS) is well established and has been shown to differentiate drugs,¹²⁻¹⁵ powders,¹⁶⁻¹⁸ liquids,^{16, 19-21} as well as predict dissolution rate in otherwise identical samples¹³. FTARS is nondestructive and complete scans can be made in seconds, therefore it is a prime candidate for use as a process analytical technique (PAT). However, FTARS relies on intensive computer processing following data collection due to the amount of information gained in each scan. An ARS spectrum recorded over the interval of 20 Hz to 20 kHz with a sample rate of 44.1 kHz for one second generates a substantial amount of data (1 s x 44.1 kHz = 44100 data points). Chemometric analysis of multiple FTARS data sets can become computationally demanding and could limit the production rate of tablets, especially if 100% tablet inspection is considered. ISP-ARS reduces the computational burden of FTARS because it directly produces the analyte identity as an output.

Theory

In FTARS, white noise comprising a mixture of all frequencies over a specified range is used as excitation for scanning a calibration set of samples. If no *a priori* information is given about the samples then sample classification is made via undirected (unsupervised) data mining. For this qualitative tablet identification experiment, multivariate techniques are employed to group the calibration data into specific classes. The specific classes are then used to build a predictive model on which ISP-ARS is based. To begin, a training set of data is scanned over the entire frequency range using FTARS techniques. Principal component analysis (PCA) is employed to separate the samples into classes. PCA is a

multivariate analysis technique that reduces the amount of data in large sets. PCA has been previously applied to FTARS and other spectroscopic data to differentiate samples^{13, 15-16, 22-23}. In PCA a new set of data, the principal components (PCs), are generated from the acoustic frequencies such that the first PC contains the most variation of the original data, the second PC the next highest variation orthogonal to the first, and so on until the total sample variation is explained. If there is a significant amount of correlation present in the original data then the number of useful PCs is small²⁴. The PCs that denote the greatest variation among the calibration set tablets are used to create the ISP acoustic waveforms. The loadings (coefficients) of the PCs are used to indicate the frequency regions that have the greatest effect on each PC (Fig. 2). In ISP-ARS, the acoustic waveforms are created from those frequency regions where the greatest sample variation was observed, and that had the largest loading coefficients. The PC loadings, however, are weighted in both the positive and negative direction, which is due to positive and negative differences among the spectra (see Fig. 2, part A & B), and each contains useful information. Thus, loadings over the frequency region corresponding to the highest variation in the data must be found in both the positive and negative directions. Separate acoustic waveforms must be created for the positive and negative loading data. If the data are not separated then frequency components from the positive data domain may offset the components from the negative when the entire time domain waveform is integrated during the detection process. This is because excitation of the analyte with positive loading frequencies will have a specific effect on the acquired voltage data while the negative loading frequencies will have an opposing effect on the voltage data. The same is true for each specific PC loading that is used; frequency components from one loading may overlap with components of another. In many cases, a single PC is sufficient for a tablet analysis. But suppose that in practice it is found that the top three PCs separate the tablet calibration data sufficiently. The corresponding loadings for PCs 1-3 must be broken into positive and negative pieces, and an ISP acoustic waveform constructed from three PCs would have six segments that would be played sequentially and integrated into six distinct detector values. Cluster analysis of the detector voltage data would complete the

Fig. 2 In a series of samples (B) the highest variation in frequency range of interest can be viewed in the highest loadings (A). Selection of the greatest frequencies from the positive and negative component of the loadings (C) can be used to construct the ISP waveform (D). To avoid cancellation of integrated signal from positive and negative loading frequencies, an acoustic waveform must be constructed separately for the positive and negative loadings and transmitted independently through the sample.



classification of a sample. One method of classifying the output voltages is the Bootstrap Error-adjusted Single-sample Technique (BEST). The BEST method of sample classification calculates the distance between data clusters in multidimensional standard deviations (MSD)²⁵. When distance of a spectrum from a cluster is less than three MSDs, the unknown spectrum is considered to be of the same sample as the cluster. ISP acoustic waveforms can be generated from many samples, and an MP3 player can be used to hold an entire database of ISP excitation waveforms. This makes ISP-ARS a great choice for PAT as pharmaceutical manufacturers could calculate an ISP acoustic waveform from FTARS data to determine many sample properties and characteristics in their production line.

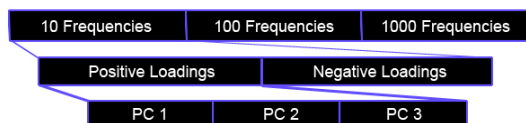
EXPERIMENTAL

Materials. Tablets of different over-the-counter pharmaceutical drugs were obtained for scanning by the ARS. The Tablets analyzed included: vitamin C (Spring Valley, 1000 mg), vitamin B-12 (Spring Valley, 2000 mcg), acetaminophen (Equate, 325 mg), aspirin (TopCare, 325 mg), ibuprofen (Equate, 200 mg) and D-tagatose (Spherix Inc, 300 mg). The tablets were scanned intact with no special preparation except for D-tagatose which was pressed in-house. The physical properties of each tablet scanned varied from one another. Vitamin B-12 and C were similar in shape and size but

were of greater mass than all other tablets. The pain relievers also had similar shapes and sizes (common solid round tablets). However, slight differences in the physical and chemical properties of the tablets contributed to differences in the AR spectra.

ARS Data Collection. Four tablets each of the pharmaceutical drugs were scanned along with a blank (a scan of the empty base-plate at equal pressure as the tablets), in triplicate and in random order. Each tablet was placed on a scale (Model 3120, Health O Meter, Bridgeview, IL, USA) and adjusted to a pressure of 150g so that contact between the sample and the quartz rod of the ARS was maintained and constant throughout scanning. After each scan, the scale was reset and the tablets repositioned. White noise in the frequency range of 0 to 3.1 MHz was generated using a function generator (Stanford Research Systems, Sunnyvale, CA, USA). The sound card used to capture the data (Model No. SB0490, Creative Labs) had a range of 20 Hz to 22 kHz and the card contained an anti-aliasing filter that prevented problems from excitation outside the frequency range of the function generator. All data processing was done in Matlab 7.0.1 (The Mathworks Company, Natick, MA, USA). The tablet spectra were obtained over 5 seconds with a sample rate of 44.1 kHz producing 220,500 (44.1 kHz x 5s) data points for each scan. The time domain data was transformed to the frequency domain using the Fourier Transform (FT) so that each resulting

frequency spectrum contained 22,050 data points. The mean of each three replicate measures was taken. Frequency domain data were z-scored in intensity and principal axis transformation was performed on the data before cluster analysis. Loadings from the first three PCs were used to find the frequencies that contributed the most to the total variance between sample types. The positive and negative loadings were separated and sorted by principal component number in descending order. The frequencies corresponding to the largest 10, 100 and 1000 loading values encompassing a single resonance peak were used to create the excitation signal for ISP-ARS. The excitation signal consisted of 18 frequency ensembles in sequence, one second of each. The first three frequency ensembles were from the positive loadings of PC one through three using only ten frequencies. Sequence four through six were created from the negative loadings of PC one through three using ten frequencies. The order was then repeated for 100 and 1000 frequencies to give the total of 18 ensembles (Fig. 3). The average detector voltage signal of each frequency mixture became a single dimension in the classification process. Because the excitation was performed using the frequency ensemble created from the PC loadings, the detector voltage was directly proportional to the PC scores, and multiple analyses of variance (MANOVA) using BEST MSDs was used for



classification of tablets in the ISP-space.

Fig. 3 An 18-second excitation sequence was conducted to enable the three experiments to be conducted simultaneously. The first frequency ensembles were from the positive loadings of PC one through three using only ten frequencies. The order was then repeated for 100 and 1000 frequencies, enabling three different calibration and prediction experiments (testing calibration using 10, and 1000 frequencies) to be conducted with the same tablets at the same time.

RESULTS AND DISCUSSION

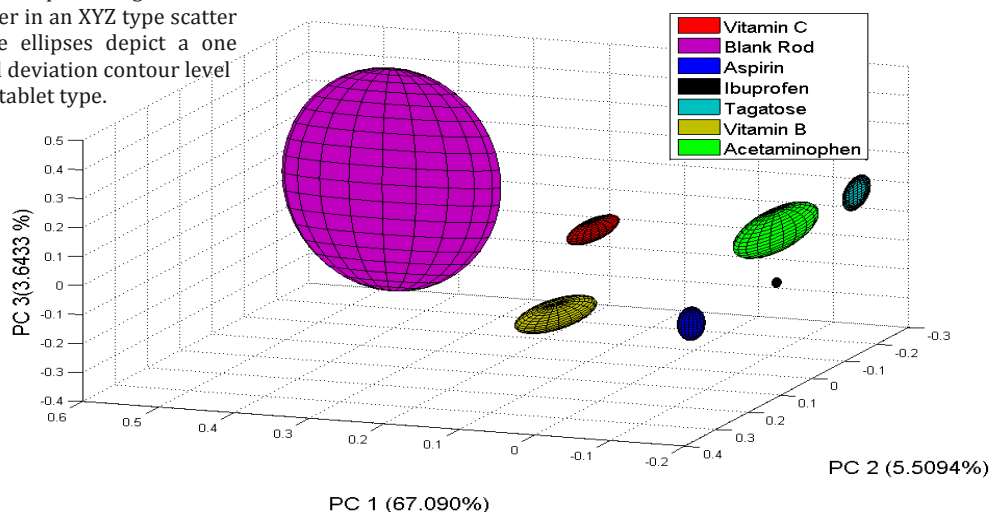
Three PCs representing 76% of the total variance of the data set was used to classify the

tablets. Of each 10, 100 and 1000 frequencies, three orthogonal excitations (one for each PC) were employed for both the positive loadings and negative loadings obtained from PC analysis. The three orthogonal excitations were visualized in a three-dimensional scatter plot (Fig. 4). Similar samples can be visualized as clusters in a three-dimensional scatter plot with dissimilar samples clustering in different regions hyperspace. When ISP waveforms were constructed from PC loadings the resultant ISP voltages observed at the detector were functionally equivalent to the PC scores.

Projecting the three integrated detector voltage signals scanned from a sample onto a three-dimensional scatter plot illustrated the group in which the sample belonged. Additional scans of the same type of tablets contained the information needed to draw probability density contour plots encompassing the regions where spectral points of more samples of the same material were likely to be found. This approach of digitally calculating PCs initially to form an excitation waveform (effectively an analog computing alternative to the more typical digital analysis after spectra have been collected) allows for a rapid data acquisition and determination of probability densities for classification [26].

ISP-ARS vs FTARS Clusters. Figure 4 illustrates the cluster patterns using conventional ARS with principal component (PC) analysis. The PCs that captured the largest variations between spectra were plotted against each other in an XYZ type scatter plot. The figure depicts the separation between the different types of tablets. Figure 5 and Figure 6 illustrate similar plots as Figure 4, but rather than calculating the PCs from full acoustic spectra, the XYZ axes represent the observed detector voltages from the ISP-AR excitations. Figure 5 represents the voltages acquired from the ten frequencies with the positive loadings contributing to the largest variation. Figure 6 represents the voltages acquired from the ten frequencies with the negative loadings contributing to the largest variation. All clusters from both methods contain 4 sample points, and the ellipses represent a one standard deviation level in each direction. Adding frequencies sometimes improved the cross validated separation between tablets, but sometimes did not (see Table 1).

Fig. 4 The PCs that captured the largest variations between spectra were plotted against each other in an XYZ type scatter plot. The ellipses depict a one standard deviation contour level for each tablet type.



Comparisons between positive loadings (Fig. 5) and negative loadings (Fig. 6) indicate that each excitation was important on different tablet types. Note that while the positive loading excitations do not separate the blank rod from tagatose and acetaminophen at the three standard deviation level, the negative loading excitations do separate them. Employing the positive and negative loadings together in the analysis allows the benefits of both to separate the different types of tablets. Canonical Variables (CV) were calculated from the voltages obtained from the ten frequencies of both the positive and negative loads to produce Figure 7. The ellipses in Figure 7 depict a three standard deviation contour level.

Fig. 5 The coordinate axes represent the detector voltages from the ISP-AR spectra. This figure represents the voltages acquired from the ten frequencies with the positive loadings contributing to the largest variation in the FTARS scans. The ellipses here depict the one standard deviation contour level for each tablet type.

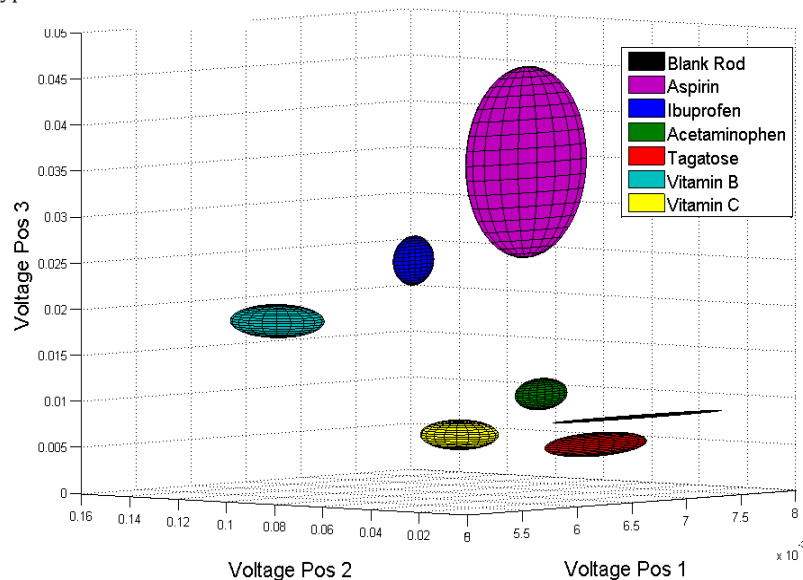


Table 1 reports the mean inter-cluster and intra-cluster BEST multidimensional standard deviations (MSD) for the different tablets. The mean intra-cluster MSDs from cross validation are reported on the diagonal in bold face type. ISP-ARS represents a slight improvement over full spectrum FT-ARS, but some intra-cluster MSDs are increased with more frequencies in the excitation process, while others are being decreased (overfit) with more frequencies in the excitation process. Neither FT-ARS nor ISP-ARS have all intra-cluster MSDs below three standard deviations, probably due to the low number of tablets scanned in each group (four). However, ISP-ARS does lead to larger inter-cluster MSDs than FT-ARS. For example, for FT-ARS the largest inter-cluster distance is 176.903 between ibuprofen and the blank rod, and that same inter-cluster distance with ISP-ARS is 236.694 (with 10 frequency,

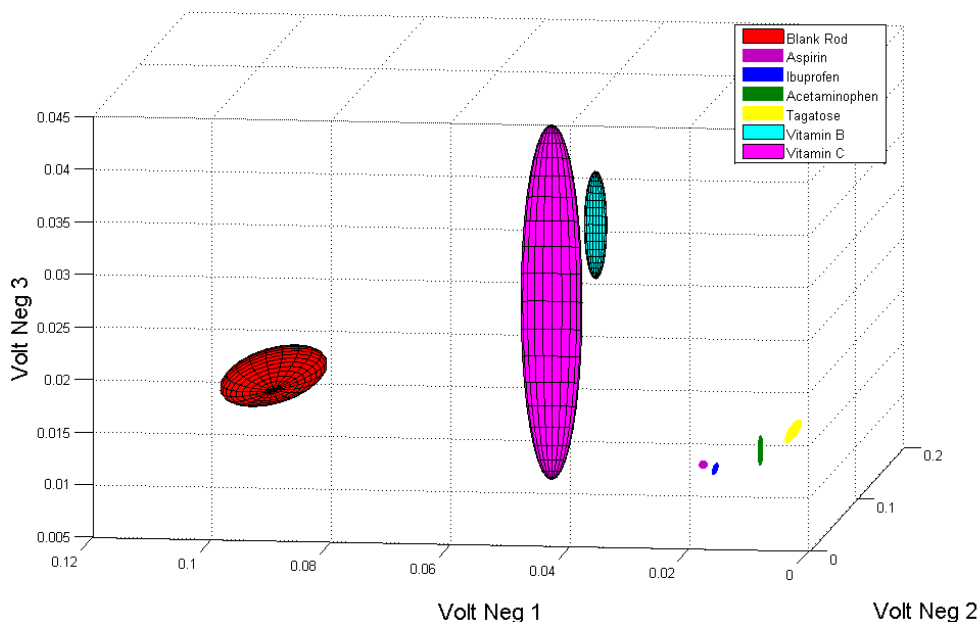


Fig. 6 The coordinate axes depict the detector voltages from the ISP-AR spectra. This figure represents the voltages acquired from the ten frequencies with the negative loadings contributing to the largest variation in the FTARS scans. The ellipses here depict the one standard deviation contour level for each tablet type.

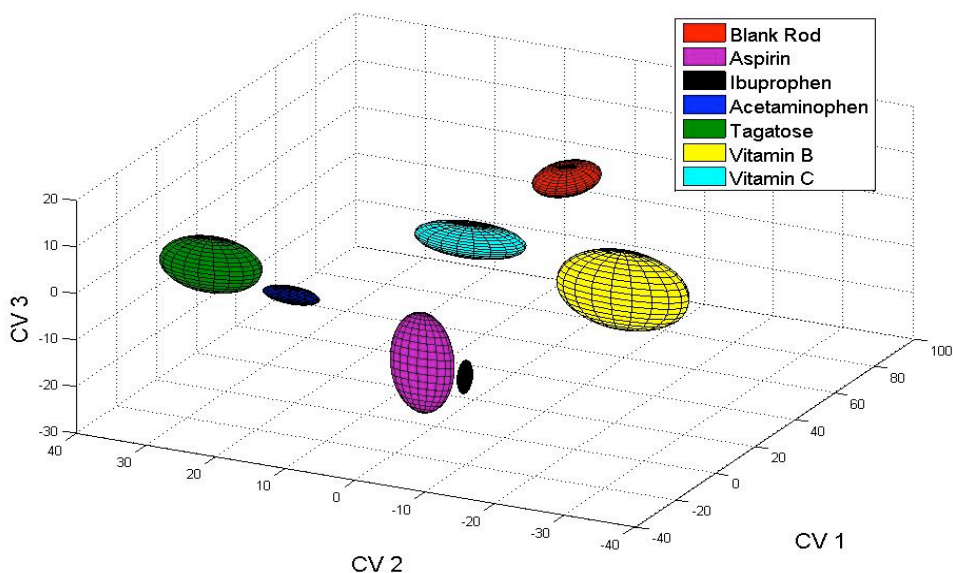


Fig. 7 Canonical Variables (CV) from the voltages obtained from the 10 frequencies of both the positive and negative loadings. Ellipses depict the three standard deviation contour level for each tablet type.

positive and negative loadings excitation). Because there are such large inter-cluster MSDs with ISP-ARS, it would be possible to increase MSD distance cutoff for classification to the largest intra-cluster MSD, as long as it is much smaller than the smallest inter-cluster MSD, and still maintain accurate classification.

ISP-ARS Classifications. MANOVA was used for cross validation classification where each tablet was classified to clusters three standard deviations or less away. Tables 2, 3 and 4 report classification, accuracy, precision and recall when using 10 frequencies, 100 frequencies and 1000 frequencies respectively in

TABLE 1 (continued)

ISP-ARS 10 Frequencies							
	Blank	Asp	Ibu	Acet	Tag	Vit B	Vit C
Blank	3.234	292.776	236.694	586.349	122.096	90.723	71.394
Asp	-	2.180	109.896	56.738	28.600	23.160	42.752
Ibu	-	-	1.448	39.902	28.230	18.336	42.202
Acet	-	-	-	1.685	8.667	33.079	37.650
Tag	-	-	-	-	2.411	50.455	47.551
Vit B	-	-	-	-	-	2.056	36.598
Vit C	-	-	-	-	-	-	5.312
ISP-ARS 100 Frequencies							
	Blank	Asp	Ibu	Acet	Tag	Vit B	Vit C
Blank	1.875	49.635	56.821	142.394	165.027	35.000	34.604
Asp	-	3.489	12.338	81.420	34.759	36.403	58.583
Ibu	-	-	1.548	49.770	19.618	21.577	39.843
Acet	-	-	-	5.121	7.886	20.616	14.339
Tag	-	-	-	-	2.441	23.366	14.283
Vit B	-	-	-	-	-	1.582	29.977
Vit C	-	-	-	-	-	-	2.423
ISP-ARS 1000 Frequencies							
	Blank	Asp	Ibu	Acet	Tag	Vit B	Vit C
Blank	4.248	190.660	106.067	125.373	150.548	79.002	69.626
Asp	-	8.608	19.628	71.496	100.572	36.624	88.467
Ibu	-	-	2.458	78.743	90.821	35.275	84.459
Acet	-	-	-	2.242	44.920	29.948	32.958
Tag	-	-	-	-	3.942	49.826	35.770
Vit B	-	-	-	-	-	2.381	62.774
Vit C	-	-	-	-	-	-	2.786

Table 2: Summary statistics for ISP-ARS utilizing both the ten frequencies with the greatest change according to the positive factor loadings and the 10 frequencies with the greatest change according to the negative loadings. MANOVA was used for the classification and each tablet was classified to any group within three standard deviations in hyperspace.

Group	Correct Classification	Accuracy (%)	Precision (%)	Recall (%)
Blank	3	96.43	100.00	75.00
Asp	4	100.00	100.00	100.00
Ibu	4	100.00	100.00	100.00
Pain	4	100.00	100.00	100.00
Tag	4	100.00	100.00	100.00
VitB	4	100.00	100.00	100.00
VitC	2	92.86	100.00	50.00
AVERAGE	3.57	98.47	100.00	89.29

Table 3: Summary statistics for ISP-ARS utilizing both the 100 frequencies with the greatest change according to the positive loadings and the 100 frequencies with the greatest change according to the negative loadings.

Group	Correct Classification	Accuracy (%)	Precision (%)	Recall (%)
Blank	4	100.00	100.00	100.00
Asp	2	92.86	100.00	50.00
Ibu	4	100.00	100.00	100.00
Pain	2	92.86	100.00	50.00
Tag	3	96.43	100.00	75.00
VitB	4	100.00	100.00	100.00
VitC	4	100.00	100.00	100.00
AVERAGE	3.29	97.45	100.00	82.14

CONCLUSION

Integrated sensing processing acoustic resonance spectroscopy has been explored as a rapid and non-destructive method to differentiate D-tagatose (an experimental toll-manufactured drug) and other toll manufactures tablets, including aspirin, acetaminophen, vitamin C, vitamin B and ibuprofen. With an experiment-specific ISP waveform, the classification is far more rapid than with conventional ARS. Simpler ISP waveforms using fewer frequencies to represent the factor loadings that separate the tablets may outperform more complex waveforms using more frequencies. By encoding waveforms on an MP3 player, ISP-ARS could become a method to quickly identify different unlabeled tablets with a similar appearance created in a contract-manufacturing environment.

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